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Large animal models for translational research in acute kidney injury

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ABSTRACT

While extensive research using animal models has improved the understanding of acute kidney injury (AKI), this knowledge has not been translated into effective treatments. Many promising interventions for AKI identified in mice and rats have not been validated in subsequent clinical trials. As a result, the mortality rate of AKI patients remains high. Inflammation plays a fundamental role in the pathogenesis of AKI, and one reason for the failure to translate promising therapeutics may lie in the profound difference between the immune systems of rodents and humans. The immune systems of large animals such as swine, nonhuman primates, sheep, dogs and cats, more closely resemble the human immune system. Therefore, in the absence of a basic understanding of the pathophysiology of human AKI, large animals are attractive models to test novel interventions. However, there is a lack of reviews on large animal models for AKI in the literature. In this review, we will first highlight differences in innate and adaptive immunities among rodents, large animals, and humans in relation to AKI. After illustrating the potential merits of large animals in testing therapies for AKI, we will summarize the current state of the evidence in terms of what therapeutics have been tested in large animal models. The aim of this review is not to suggest that murine models are not valid to study AKI. Instead, our objective is to demonstrate that large animal models can serve as valuable and complementary tools in translating potential therapeutics into clinical practice.

Abbreviations: AKI: acute kidney injury; DAMPs: Danger-associated molecular patterns; GFR: Glomerular filtration rate; iNOS: Inducible nitric oxide synthases; I/R: Ischemia reperfusion; IRI: Ischemia reperfusion injury; LAM: Large animal models; LPS: Lipopolysaccharides; MSC: Mesenchymal stem cell; NHP: Nonhuman primates; NO: Nitric oxide; PAMPs: Pathogen-associated molecular patterns; PRR: Pattern recognition receptors; TLR: Toll-like receptors

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Introduction

Acute kidney injury (AKI) is defined by a sudden reduction in renal function and is associated with mortality in observational studies. For example, one study of combat casualties found that AKI was independently associated with mortality after adjustment for demographics, hemodynamics, and injury severity [1]. Furthermore, AKI has been associated with long-term complications to include chronic kidney disease [2], end stage kidney disease [2], hypertension [3,4], heart failure [5,6], and mortality [7,8]. Both local and systemic inflammation plays an essential role in the pathogenesis of AKI. Despite extensive research and significant progress made in understanding basic mechanisms for the disease in rodent models, no clinically proven interventions exist to prevent AKI, accelerate recovery of AKI, or reduce progression of AKI to CKD in patients [9].

Owing to their ease of handling, breeding, and genetic modification, mice and rats are often chosen to study the basic mechanisms of AKI and to evaluate potential therapeutics. However, many promising interventions for AKI found in mice and rats have not been reproduced in clinical trials. For example, N-acetylcysteine has been demonstrated to prevent AKI induced by ischemia/reperfusion (I/R) [10], sepsis [11], rhabdomyolysis [12], and contrast medium [13] in rodents, but failed to prevent AKI induced by contrast [14], vancomycin [15], and I/R following cardiac surgery [16–18] in clinical trials. Many reasons are postulated for the failure to transition therapeutics from animal models to clinical practice [19,20], but one factor is that rodents and humans have developed different innate and adaptive immune systems, since they diverged somewhere between 65 and 75 million years ago. For instance,

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humans have 50–70% neutrophils and 20–40% lymphocytes, whereas C57BL/6 mice contain only 10–25% neutrophils, approximate 2% monocytes and 75–90% lymphocytes [21].

In the absence of a basic understanding of the molecular pathophysiology of human AKI, large animal models (LAMs) such as porcine, simian, ovine, canine, and feline models are attractive to test novel therapies, because their immune systems more closely resemble the human's when compared to rodents [22–25]. The FDA recommends that an intervention be tested in more than one animal models before the submission of an investigative new drug application (https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/animal-model-qualification-amqp-program). It is a preferred practice that at least one of these models be conducted in large animals. There are many excellent reviews of therapies tested for AKI in mice and rats in the literature. However, there is a lack of such reviews in LAMs. This review will first focus on the differences in innate and adaptive immunities among rodents, large animals, and humans in relation to AKI. After illustrating the value of LAM in testing potential therapies for AKI, this review will then summarize what has been learned from such models to date.

Overview of molecular mechanisms of AKI

The most common cause of AKI is ischemia–reperfusion injury (IRI) induced by transplantation, trauma, burns, or sepsis, that leads to a reduction of renal blood flow. The second most common cause is certain medications and toxins [26,27]. Regardless of the initial insult, however, these different causes share some common pathophysiology. While the exact sequence of events can differ, the pathophysiology includes inflammation, immune damage, oxidative stress, reduction in renal perfusion, and both apoptotic and necrotic cell death [28–31]. Following the insult, damaged cells in the kidney and/or other tissues release danger-associated molecular patterns (DAMPs), such as high mobility group box-1, S100A8, fibronectin, and DNA. In the case of sepsis-induced AKI, pathogens release pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS). The released DAMPs and PAMPs then bind pattern recognition receptors (PRR), including Toll-like receptors (TLR), on the surface of kidney cells and leukocytes and activate NF-κB and other pro-inflammatory transcription factors. This results in the release of cytokines and chemokines with subsequent adhesion and infiltration of leukocytes into the renal parenchyma, culminating in endothelial dysfunction, impaired mitochondrial function, disturbed redox balance, epithelial apoptosis, and necrosis. After these pathologic changes reach a threshold, kidney function is compromised as evidenced clinically by oliguria as well as increases in serum creatinine and blood urea nitrogen [28,31–33].

The differences in innate immunity among rodents, large animals, and humans

Given the acute nature of AKI, innate immunity is a predominant driving factor in its pathophysiology. Innate immunity is composed of soluble molecule-mediated immunity and cell-mediated immunity. The former includes complement, cytokines, and chemokines, while the latter includes macrophages, neutrophils, natural killer, and dendritic cells [34,35]. The infiltration of innate immune cells into the kidney is coordinated by a large array of chemokines. It has been reported that the chemokines CCL24/CCL26, CXCL8/IL-8, CXCL7, CXCL11, CCL13, CCL14, CCL15, CCL18, and CCL23 and are present in humans, but not in mice. Conversely, CCL12, CCL6, CCL9, and CXCL15 have been identified in mice, but not in humans [21]. Some of these chemokines have been demonstrated to be important for the development of AKI. For example, CCL24/CCL26 is increased in patients with subclinical and clinical rejection of kidney allograft in patients [36].

Neutrophils are the most abundant type of granulocytes and make up 40–70% of all white blood cells in humans. They are also the most abundant leukocytes infiltrating the kidney immediately after IRI [37]. Neutrophils produce and secrete cytotoxic compounds such as reactive oxygen species, while adhering to the endothelium and extravagating into the affected renal tissue. CXCL8/IL-8 is the primary chemoattractant for human neutrophil recruitment. Serum CXCL8/IL-8 levels predict AKI in patients with acute pancreatitis [38], after cardiac surgery [39] and liver transplantation [40]. Conversely, CCL12 probably mediates tubular regeneration and functional recovery from cisplatin-induced AKI following inhibition of dipeptidyl peptidase-4 in a murine model [41]. Given the important roles that these molecular pathways play in the development of AKI, it becomes apparent that immunomodulatory findings from rodent AKI models may have certain limitations [19].

Macrophages are the most abundant immune cells within the kidney, but monocytes are rare in the healthy kidney. After recruitment into the injured kidney, monocytes differentiate into proinflammatory M1 and/or immune-regulatory M2 types of macrophages

[42]. Although the exact stimuli and mechanisms causing differentiation into M1 versus M2 macrophages remain unclear, binding of DAMPs and PAMPs to PRR induces activation of M1 macrophages from both resident and differentiated macrophages. Activated M1 macrophages then secrete proinflammatory cytokines such as IL-1β, IL-6, IL-12, IL-18, and TNF-α, and release reactive oxygen and nitrogen species, which contribute to AKI. M2 macrophages release anti-inflammatory mediators such as IL-10 and TGF-β, limiting inflammatory responses in the kidney. Inducible nitric oxide synthase (iNOS) is the primary source of reactive nitrogen species in macrophages in mice [34,43]. In murine macrophages, iNOS is up-regulated by several orders of magnitude upon incubation with IFN-γ or LPS. In contrast, iNOS is not generally present in human macrophages; although there are some reports showing expression of iNOS under severe disease conditions [44]. Instead, IFN-γ and LPS stimulate indoleamine 2,3-dioxygenase (IDO), an anti-inflammatory enzyme, in human macrophages [44]. Furthermore, the lethal dose of LPS for mice is about 1000 times higher than that for humans [44].

These differences must be taken into consideration when translating potential therapeutic candidates that target macrophages which have been identified in murine models. For example, Rasburicase prevents cisplatin-induced AKI in rats in part through reduction of macrophage infiltration [45]. However, it failed to prevent AKI after cardiovascular surgery in patients [46]. Probiotics ameliorate I/R-induced AKI by increasing M2 macrophages in rats [47]. However, it has been demonstrated that the density of $CD163^+$ M2 macrophages in the human kidney correlates with the severity of a variety of renal diseases, including: AKI [48], acute tubular injury [49], IgA nephropathy [50], chronic kidney allograft injury [51], and lupus nephritis [52]. Moreover, erythropoietin prevents AKI in various murine models in part by reducing the infiltration of macrophages and promoting M2 macrophage phenotype [20,53]. However, it has failed in the majority of clinical studies [20,44].

In contrast to rodents, the immune systems of large animal animals are more analogous to humans. Similar to humans, dogs and pigs have intralobular lymphatics, which is absent or not yet defined in mice [54]. Among LAM, pigs are the most popular large animals used in the kidney research (Figure 1). Pigs share more than 80% of immune parameters with humans as compared to mice that share less than 10% [22,23,55]. Similar to humans, and in contrast to mice, pigs have a high percentage of neutrophils in the peripheral blood (50–70%), express CXCL8/IL-8, do not express iNOS in macrophages, IFN-γ and LPS stimulate IDO in macrophages, and pigs are sensitive to endotoxin shock [23,56]. As in humans, expression of CXCL-8/IL-8 and infiltration of M2 macrophages correlate with disease severity in pigs. This is evidenced by studies in swine showing that attenuation of burn- and trauma-induced AKI by oral resuscitation and vitamin C is associated with a reduction of serum levels of CXCL-8/IL-8 [57,58] and that mitigation of I/R-induced AKI by inhibiting complement pathway is associated with decrease of infiltration of $CD163^+$ M2 macrophages into the kidney [59].

TLR4, the receptor for LPS, is arguably the most important receptor of PRR. Swine and human TLR4 genes have approximately 83% sequence homology in three exon sequences as opposed to 75% between humans and mice. Overall, the porcine TLR4 promoter

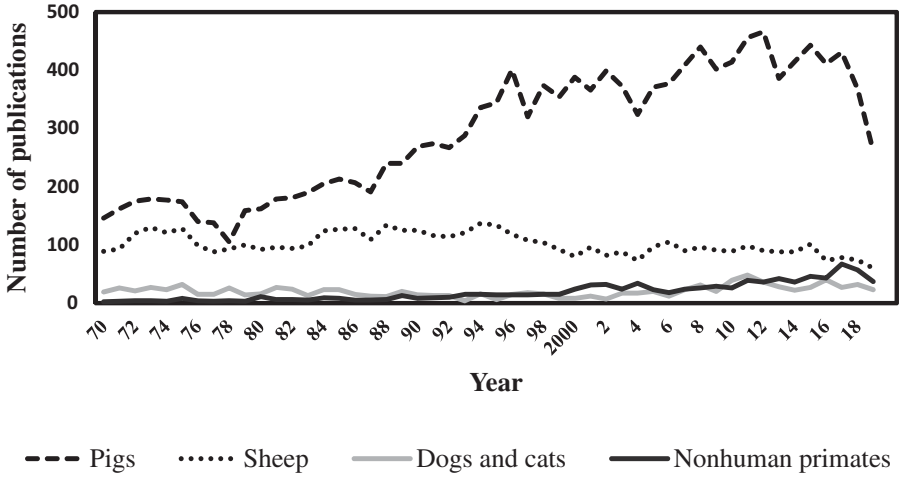

Figure 1. Large animal models in kidney research indexed in the PubMed from 1970 to 2019. (Year X-axis) retrieved using a search query: ('renal' OR 'kidney') AND ('species name') on May 20, 2020. The overall trend shows the preference for porcine models.

shares more features with the human TLR4 promoter than its murine counterpart [60]. Moreover, porcine and human kidneys express similar level of TLR4 protein, whereas the murine kidney expresses twice as much [61]. TLR signaling is MyD88-dependent with the exception of TLR3. The putative porcine MyD88 protein shares a higher level of homology with its human (87.2% amino acid identity) than with its mouse (77.4% amino acid identity) counterpart [62].

In terms of nonhuman primates (NHPs), comparison of the chimpanzee and human genomes has revealed remarkable conservation of genes; about 30% are identical and single base pair substitutions account for about half of the genetic change [63]. Chimpanzee and human TLR4 gene sequences only have differences at three amino acid positions [24,25]. Features of the innate immune system are not where the similarities stop between large animals and humans, but these commonalities also extend to the adaptive immune system.

The differences in adaptive immunity among rodents, large animals, and humans

Adaptive immunity is mediated by T and B lymphocytes. Although there is some discrepancy, the majority of studies have demonstrated or suggested that $CD4^+$ T cells are a factor in driving the initial phase of AKI in murine models, whereas the roles of cytotoxic T cells and B cells remain unclear [64]. Whether $CD4^+$ T cells are involved in human AKI is unknown, but in pig models of renal autotransplantation, addition of polyethylene glycol, trimetazidine, and/or an inhibitor of complement to preservation solutions decreases infiltration of macrophages and T or $CD4^+$ T cells into the kidney, and results in reduced graft injury [65–68]. Depending on inducers, $CD4^+$ T cells can be activated and differentiated into different subsets including pro-inflammatory Th1 and Th17 cells and regulatory T cells (Treg) [64]. In rodents, both Th1 and Th17 subsets contribute to AKI through secreting pro-inflammatory cytokines and recruiting other types of pro-inflammatory cells into the kidney, whereas Treg cells protect the kidney from IRI and help resolution of AKI by limiting inflammation [64,69,70].

An important difference in $CD4^+$ T cell activation exists between mice and humans. In order to fully activate $CD4^+$ T cells, the costimulatory receptor CD28 has to be activated. Nearly all mouse $CD4^+$ T cells express CD28, whereas only 80% of human $CD4^+$ T cells express CD28 on their surface [21]. Several studies have shown that blocking the CD28 costimulatory pathway with CTLA-4 Ig decreases infiltration of monocytes and ameliorates I/R-induced AKI in rodents [71–73]. However, CTLA-4 Ig does not significantly affect human Th1 cells in renal graft tissue [74]. Moreover, immunotherapy with CTLA-4 antibodies causes AKI in some cancer patients [75,76].

Differences also exist at the differentiation and phenotypic levels between rodent and human T cells. In humans, type I interferon IFN-α stimulates Th1 differentiation, whereas it does not in mice [21]. The human Th17 cells express surface CCR2, whereas mouse Th17 cells express CCR7 instead [77]. Human Th17 cells have multiple subsets, whether similar subsets exist in rodents is not clear [78,79]. Mouse immune tolerance is a poor predictor of human tolerance [80]. However, this gap can be alleviated by NHP Treg cells, which display phenotypic and functional similarities with human Treg cells [81]. Taken together, differences in immunology between humans and mice may help explain the lack of successful pharmacotherapies for AKI in patients.

The differences in gut microbiota among rodents, large animals, and humans

Gut microbiota regulates immune responses in pre-clinical models and humans [82,83]. Emerging evidence indicates that gut microbiota also plays a critical role in modulating various renal diseases [84,85]. The majority of our current knowledge of the effects of gut microbiota on AKI is from studies using mice and rats, and data from LAM studies are scarce [85–87]. There is a positive correlation between gut *Rothia* and *Staphylococcus* levels and renal function in a rat I/R AKI model [88]. Depending on experimental contexts, both reno-protective and reno-harmful effects of gut microbiota have been reported. Germ-free mice have an unexpectedly high frequency of natural killer T cells and abundant T cells in the kidney and are prone to I/R-induced AKI [64]. In contrary, depletion of mouse gut microbiota by an antibiotic-cocktail significantly attenuates I/R-induced AKI associated with low expression of F4/80 macrophages and pro-inflammatory chemokines [89]. Intestinal microbiota modulates immune reactions in AKI through their metabolites such as short chain fatty acids, trimethylamine-N-Oxide, and D-amino acids [86,90]. While it is known that there is a gut-kidney cross talk, it has only recently been demonstrated that AKI can influence intestinal microbiomes. Traditionally, I/R-induced AKI has been regarded as sterile inflammation. However, Yang *et al* recently reported that I/R-induced AKI provokes intestinal dysbiosis and bacterial translocation which is associated with increases of Th1

and Th17 responses as well as activation of neutrophils and M1 macrophages in a mouse model. It is possible that the translocation of gut resident bacteria exacerbates inflammatory process in I/R-induced AKI [91].

Because gut microbiota modulate immune responses in AKI, manipulating the gut microbiota has been proposed as a possible new therapeutic avenue to treat AKI. D-serine, a gut microbiota metabolite which is decreased in AKI patients, mitigates I/R-induced AKI in mice when given orally [90]. Anticipating further studies in this area, it is important to recognize the differences amongst murine, large animal, and human gut microbiota [92]. Although mice and humans share considerable anatomical, histological, and physiological similarities of the intestinal tract, the differences in the size of intestinal tract and dietary habits contribute to only 4% of shared bacterial genes in mice and humans [93]. For example, mice harbor segmented filamentous bacteria, which have a profound effect on the maturation of innate immune system, whereas these bacteria have not been identified in human adults [93]. On the other hand, *Macaca fascicularis* shares 39.49% of gut microbiome genes with humans and 25.45% of the genes with pigs; this is compared with only 0.6% of the genes with mice [94]. Like humans, the pig gut microbiota mainly consists of Formicates and Bacteroidetes phyla [95]. Further, human microbiota-associated piglets have been established by inoculating microbiota from infants, children, and adults. These piglets share even more gut microbiota with humans than conventional piglets [96]. Since gut microbiota regulate immune responses, the differences in murine and human gut microbiota compositions could contribute to the differences in immune responses seen during AKI. Likewise, similarities between large animal and human microbiota may explain some of the shared characteristics in AKI-induced immune responses.

Mechanistic strategies of AKI for evaluating therapeutics in LAM

The strategies that have been evaluated to intervene on AKI in LAM are similar to those evaluated in mice and rats [30]. They include limiting inflammation, reducing oxidative stress, increasing renal blood flow, and stem cell therapy. Multiple approaches targeting various steps in immune pathways have shown promising results in LAM (Tables 1–4). They include inhibition of TNF-α by an antibody in NHP [165] and the chemical FR167653 in pigs [112], infiltration of macrophages, and T-helper cells by the chemical TBC-1269 in pigs [105], and complement cascade by compstatin CP40 in cynomolgus monkeys [153]. Erythropoietin is well known for its erythropoietic effect and was later recognized to be an anti-inflammatory cytokine. Erythropoietin acutely improves glomerular filtration rate (GFR) in pigs after IRI and reduces both renal and circulating levels of TNF-α [106]. Erythropoietin also shows a preventive effect against AKI in NHP [156]. The side effect of increased red blood cells, and higher levels of hematocrit, can be minimized by an 11 amino acid nonerythropoietic peptide (ARA290) without losing anti-inflammatory properties [109]. Further, ARA290 reduces interstitial fibrosis by decreasing α-smooth muscle actin in the porcine kidney [109]. However, only two out of nine clinical trials found the preventive effect of erythropoietin against I/R-induced AKI in patients, indicating that even LAM is not a complete replica of humans in the translational research [20].

Strategies that target the underlying cause of AKI may also be effective in inhibiting inflammation, which can potentially be discovered by the use of LAM. For example, an exciting recent avenue of interest in the trauma field involves the role of endotheliopathy in inflammatory processes [194,195]. This is mediated in part by glycocalyx shedding which predisposes the vasculature to cellular extravasation into the interstitial space. This has been examined in models of both cardiopulmonary bypass [196] and burns [197], as both renal and circulating markers of glycocalyx shedding (e.g. syndecan) are implicated in the development of AKI. In the context of burn trauma, it is known that resuscitation fluid can affect the degree of endothelial dysfunction [198]. However, it is also known that hypovolemia plays a role in burn-induced AKI, and fluid resuscitation ameliorates burn-induced AKI and is associated with decreases in IL-1β, IL-6, IFN-γ, and GM-CSF in pigs [150].

Oxidative and nitrostative stresses also mediate AKI. Sodium sulfides or hydrogen sulfide attenuate I/R-induced AKI in a porcine model by reducing nitrostative stress, lipid peroxidation, IL-1β, and IL-6 [118]. Rapamycin mitigates AKI by reducing lipid peroxidation, protein carbonylation, NF-κB and by promoting mitophagy in a mini-pig model [140]. Mitochondria are a major source of reactive oxygen species which may be ameliorated by Elamipretide, which is a mitochondria-targeted tetrapeptide. By decreasing ROS generation and stabilizing cardiolipin [199], an important component of the inner mitochondrial membrane, Elamipretide improves renal function in atherosclerotic renal artery stenosis-induced injury in domestic pigs [137].

Table 1. Major therapeutic approaches tested in porcine models.

Model	Therapy	Therapeutic target	References
Ischemia Reperfusion	Doxycycline	MMP inhibition reduces lipid peroxidation	[97]
	Carbon monoxide inhalation	Activates HSP70 response, anti-apoptosis, anti-inflammatory	[98]
	Sitaxentan	Endothelin-A-receptor antagonist improves hypoxia	[99]
	Sildenafil citrate	Increases NO bioavailability and reduces inflammation	[100]
	Ulinastatin	Antioxidative stress, anti-inflammatory	[101,102]
	Alkaline phosphatase	Dephosphorylation of signaling molecules, adenine, etc.	[103]
	Canrenoate	Reduces oxidative stress	[104]
	TBC-1269	Selectin ligand blockade prevents leucocyte adhesion	[105]
	Erythropoietin	Anti-inflammatory decreases TNF-α	[106]
	Erythropoietin	Reduces noradrenaline requirements to achieve the hemodynamic targets	[107]
	Carbamylated erythropoietin or recombinant human erythropoietin	Failed to attenuate prolonged ischemia-induced AKI	[108]
	ARA290, EPO derivative	Reduces MCP-1 and IL-6 and interstitial fibrosis	[109]
	Cyclic helix B peptide	Antiapoptosis, tissue protection	[110]
	AP214	α-MSH analogue, anti-inflammatory	[111]
	rhC1 inhibitor	Inhibits complement system	[59]
	FR167653	P-38 MAPK inhibitor reduces TNF-α	[112,113,114]
	Anti-high-mobility group box 1 antibody	Reduces blood inflammatory cytokine levels	[115]
	Caspase-3 siRNA	Inhibits apoptosis	[116]
	hemoreperfusion with leucocyte-depleted blood	Inhibits inflammation and apoptosis	[117]
	Hydrogen or sodium sulfide	Reduces oxidative stress, inflammatory cytokines, iNOS	[118,119]
	Hydrogen gas	No effect	[120]
	Anti-CD47 antibody	Reduces inflammation and apoptosis	[121]
	Atrial natriuretic peptide	Improves blood flow to the kidneys	[122]
	Fenoldopam	Dopamine D1 receptor agonist improves blood flow	[123]
	NO + corticosteroids	Reduces vascular resistance and inflammation	[124]
	Trimetazidine	Inhibits mitochondria oxidation of fatty acids	[125]
	Vitamins C and E	Antioxidant and nutrients	[58,126]
	Mesenchymal stem cells	Decreases inflammation, oxidative stress, and fibrosis	[127,128–130]
	Mitochondrial transplantation	Reduces IL-6 expression in the renal cortex	[131]
	Meclizine	Up-regulates glycolysis and reduces oxidative stress	[132]
	N-acetylcysteine	Reduces oxidative stress and improves hemodynamics	[133]
	N-acetylcysteine	Reduces oxidative stress	[134]
	Ascorbic acid + selenium + tocoferol and N-acetyl-cysteine	No effect on oxidative stress	[135]
	Resveratrol	Decreases oxidative stress and apoptosis	[136]
	Elamipretide	Improves mitochondrial function	[137]
	Danegaptide (not effective)	Targets mitochondrial Connexin 43 channels	[138]
	TRVP channel inhibitor	Increases blood flow to the kidneys	[139]
	Calcitonin antibodies	Blocks the effect of calcitonin	
Drugs (nephrotoxins)	Rapamycin	Autophagy, mitophagy, reduces ROS	[140]
	Magnesium	Improves renal function	[141]
	Retinoic acid	Autophagy activation and apoptosis inhibition	[142]
	microRNA-30c (miR-30c)	Reduces the inflammation by targeting NLRP3 inflammasome	[143]
	N-acetylcysteine	Reduces oxidative damage and enhances autophage	[144]
	Inhaled nitric oxide	Vasodialation, reduces inflammation, counteracts prostanoid pathways	[145]
Sepsis	Calcitonin antibody	Blocks calcitonin action	[146]
	Erythropoietin	No effect	[147]
	Polymyxin B hemoperfusion	Neutralize LPS	[148]
	Peritoneal negative pressure	Inhibits inflammation	[149]
Burn	Enteral fluid resuscitation	Useful in a resource poor environment, reduces circulating cytokines	[150]
Hemorrhagic shock	Aggressive care (AC)	Several treatments are combined together	[151]
	Terlipressin	Vasopressin analog improves blood pressure, reduces necrosis	[152]

Table 2. Major therapeutic approaches tested in NHP models.

Model	Therapy	Therapeutic target	Ref
Surgery and hemorrhage shock	Compstatin CP40	Complement protein C3 inhibition	[153,154]
	Artificial support to liver and kidney	Alternative to renal replacement therapy	[155]
Ischemia/reperfusion	Erythropoietin	Anti-inflammatory	[156]
	FR260330	Inhibits iNOS and inflammation	[157]
	Monoclonal antibody mAb107	inhibits proinflammatory integrin CD11b/CD18 to prevent progression AKI to CKD	[158]
	Mesenchymal stem cells therapy	Paracrine effects, trans differentiation	[159]
Drugs (e.g. Cisplatin gentamycin)	Mesenchymal stem cells therapy	Repair and renewal of cells in the kidney	[160]
	biomarkers	Not for therapy but to explore biomarkers	[161–[162]
Sepsis	Chimeric antibody against Factor-X	Block the coagulation cascade	[163]
	Cell-permeable peptide (TVP)	Degrades pathogenic toxins in lysosomes	[164]
	Anti-TNF-α antibody	Anti-inflammatory and reduces coagulation	[165]
	Fondaparinux pentasaccharide	Anticoagulant, inhibits factor Xa	[166]
	Diethylenetriamine pentaacetic acid	Chelates iron and reduces oxidative radicals	[167]

Table 3. Major therapeutic approaches tested in ovines.

Model	Therapy	Therapeutic target	Ref
Sepsis	TAK-242 inhibitor of Toll like receptor 4 (TLR4)	Interrupts LPS activation	[168]
	Dexmedetomidine, α2-adrenergic receptor agonist	adjunct therapy to norepinephrine infusion, reduces IL-6, increases IL-10	[169]
	Furosemide	Diuretic increases sodium excretion, decreases oxygen consumption	[170]
	Arginine vasopressin (AVP) and norepinephrine (NE)	Improves blood pressure and renal blood flow	[171,172]
	Angiotensin II	Vasoconstrictor improves blood flow and creatinine clearance	[173]
	Various resuscitation fluids	Improves blood volume and pressure	[174–175]
IRI	Ketamine, NMDA receptor antagonists	Reduces inflammation, macrophages infiltration	[176]
	organic mononitrites of 1,2-propanediol (PDNO)	Vasodilator, improves oxygen utilization in kidneys	[177]
	Zinc	Cyto-protective, upregulates hypoxia inducible factor proteins, not clear	[178]
	Mesenchymal stem cells	Not effective in the sheep model	[179]
Cardiopulmonary bypass	Metaraminol, α1-adrenergic receptor agonist	Improves oxygenation in renal medulla	[180]
Hemorrhage shock	7.5% NaCl/6% Dextran-70 (HSD) as resuscitation fluid	Improves plasma volume, hemodynamics and safe during dehydration	[181]

Increase of blood flow to the kidney by vasodilation through increasing either nitric oxide bioavailability, endothelin inhibition, or administration of hormone and neurotransmitter analogues has been shown to ameliorate AKI in LAM. By preserving nitric oxide bioavailability and preventing regional hypoxia, Sildenafil attenuates IRI in canine and swine kidneys [100,186]. Sitaxsentan, an endothelin receptor antagonist, improves hypoxia during AKI in a porcine model [99]. Sodium nitroprusside, a nitric oxide donor, in combination with N-acetyl cysteine and phosphormidon, an endothelin-1 converting enzyme inhibitor, improves renal function after I/R injury in a canine model [188]. Fenoldopam, a synthetic D1 dopamine receptor agonist, demonstrated a prophylactic benefit against the reduction in renal blood flow and renal tubular function during acute hypovolemia in anesthetized dogs [193]. Fenoldopam has also been shown to attenuate I/R-induced AKI in a porcine model [123]. Fenoldopam was found to be beneficial in the prevention or treatment of AKI in postoperative or intensive care patients [200], but a recent review only found that its renoprotective effect is transient [201]. Both atrial natriuretic peptide and brain natriuretic peptide relax vascular smooth muscles and improve blood flow and urine output in dogs [182]. Limited clinical trials suggest that low dose

Table 4. Major therapeutic approaches tested in felines and canines.

Model	Animal	Therapy	Therapeutic target	Ref
Sepsis	Dogs	Recombinant human brain natriuretic peptide (rhBNP)	Improves renal blood flow by NO generation	[182]
IRI	Cats	Mesenchymal stem cell therapy	No therapeutic effects	[183]
	Dogs	CRRL269, guanylyl cyclase A receptor peptide activator	Reduces apoptosis, modulation of intracellular Ca2+ levels	[184]
	Dogs	Vitamin C	Antioxidant, reduces BUN values, not completely effective	[185]
	Dogs	Sildenafil	Anti-inflammatory, antioxidant and anti-apoptotic	[186]
	Dogs	Mesenchymal stem cells therapy	Repair the renal tissues	[187]
	Dogs	combination therapy (n-acetyl cysteine (NAC) +sodium nitroprusside (SNP) + phosphormidon)	Antioxidant, vasodilator, endothelin inhibitor	[188]
	Dogs	Prostaglandin E2 (PGE2)	Creatinine and urea clearances were improved but the exact mechanism is not clear	[189]
	Dogs	ATP-$MgCl_2$	Improves energy metabolism, claimed to be useful in humans also	[190]
Drug	Dogs	ATP-$MgCl_2$	Worsens the renal parameters not useful, contradicts the IRI model results	[191]
	Dogs	Atrial natriuretic factor (ANF)	Increases and maintains GFR	[192]
Hemorrhage shock	Dogs	Fenoldopam	Dopamine D1 receptor agonist, improves blood flow	[193]

of atrial natriuretic peptide might be effective in preventing or treating AKI [202].

Mesenchymal stem/stromal cell (MSC) therapy has shown promise in ameliorating AKI and stimulating cellular repair in rodents [203]. Emerging evidence has demonstrated similar results in LAM. MSC exhibit recovery and protective function associated with an increase of $FoxP3^+$ Treg in cisplatin-induced AKI in *Macaque mulatta* [160]. By reducing renal expression of NF-κB, TNF-α, IFN-γ, MCP-1, and oxidative stress, MSC restores kidney function in atherosclerotic renal artery stenosis-induced AKI in pigs [127]. The main obstacles that must be addressed with MSC are the safety, dose, source of cells, and delivery methods [187,204]. To circumvent some of these obstacles, Lerman and colleagues have shown that intrarenal delivery of MSC extracellular vesicles achieves similar results as MSC in the attenuation of AKI in pigs [128–130]. However, more research is needed.

Limitations of LAM in AKI studies

Because tools such as genetic modification, monoclonal antibodies, and commercial test kits are not as widely available in LAM as they are in murine models, LAM have been used less for mechanistic inquiries. Further, the high costs of housing, longer breeding cycle, laborious surgical procedures, and animal welfare guidelines discourage the frequent use of LAM. Moreover, the technical expertise needed to surgically manipulate these animals is also challenging. Therefore, LAM is often only utilized for studying AKI for translational purposes. This results in a lack of sufficient knowledge to understand innate and adaptive immune responses behind the results and hinders follow-up studies to refine testing.

While LAM are more similar to each other than they are to rodents, immunology, and physiology still differs among the different species. Therefore, an intervention might not be equally effective in different species of LAM. For example, MSC therapy is reported to be effective in dogs and pigs [187] but not in cats [183] or sheep [179]. Even among the same species, the same treatment can have different results in different AKI models. For example, ATP-$MgCl_2$ was reported to improve I/R-induced AKI [190] but worsen cisplatin-induced nephrotoxicity [191] in dogs. Moreover, in order to induce AKI over a short time frame, the dose of a toxin used in LAM is usually higher than the equivalent dose in humans. The above considerations suggest that a multi-species, staged approach to examine mechanism and efficacy with focused etiological uses would be beneficial.

Interventions of AKI tested in the porcine models

Use of pigs for biomedical studies was recorded as early as 162 AD when Romans dissected pigs to gain a greater understanding of human physiology [205]. Today, pigs are becoming more and more popular subjects in biomedical research including kidney research (Figure 1). In addition to the immunologic similarities described above, this is due to their out breed nature, proximity to human physical size, and similar anatomy

and physiology. Unlike herbivorous rodents, pigs are omnivorous, an advantage to studying the role of gut microbiota in human AKI [95].

Vasculature plays a pivotal role in AKI. Swine kidneys are pyramidal and multilobular with vascular structure comparable to human kidneys, while mice and rats have unilobular kidneys [206]. The anatomy of the swine kidney is actually more similar to humans than that of NHP [207]. The length of renal arteries of large animals is closer to human renal artery length than rodent renal artery length. The average human renal artery is 10.4 cm long, whereas the length of a rat renal artery is only 1.54 cm. In contrast, the average length of the renal artery is 6.1 cm for goats, 3.84 cm for monkeys, and 3.01 cm for pigs [208,209]. Further, pigs have similar renal blood flow rate, resistance index, pulsatility index, and systolic/diastolic index as humans [210]. In the renal superficial veins, humans, cats, and dogs are reported to have 'stellate veins', whereas rats have only spur like veins [211]. The porcine renal function analytes such as creatinine, blood urea nitrogen (BUN) and anion secretion [22,23,212] are comparable to human's. The size of pigs as well as other LAM allow for the serial collection of blood analysis for biomarkers. The National Swine Resource and Research Center (NSRRC) offers triple knockouts and selected transgenic porcine models to facilitate translational research and potential for xenotranplantation [213]. Many markers are available to characterize pig immune cells. Moreover, pigs have been used to troubleshoot isolation of renal progenitor cells, and have been used to examine the effectiveness of these cells [214–216].

While adult domestic pigs are large, difficult to handle, and take a long time to breed, small breeds of pigs offers an alternative that mitigate some of these limitations [206]. In porcine AKI studies, fitting a dose (or ischemic time) with AKI score curve severity is difficult because the sample size is often small. Many therapeutics and their targets that have been tested in swine models to date are summarized in Table 1. Some of the therapeutics listed in the table are preventative, pretreatment, or concomitantly administered, while others are responsive and given as treatment after AKI is established. It is worth mentioning that pigs are traditionally bred for higher fat deposition, which may be protective for AKI [217]. However, in humans obesity is a well-known risk factor for AKI [218].

Therapies tested in the NHP AKI models

The number of publications utilizing NHP in the kidney research, including AKI, is low (Figure 1). One of the reasons is that due to ethical concerns, testing will only be justified when the treatment or drug has proved effective in other models. The NHP models are often designed for combined clinical insults such as trauma, blood loss, and sepsis, therefore, the injuries are not limited to the kidney. Multiple therapies have shown to improve renal function in NHP AKI models (Table 2). They include cytokine blockade, passive immunotherapy, stem cells, and erythropoietin. Unlike mice [219] and pigs [220,221], miRNA therapies are seldom examined in NHP [222,223]. This is likely because targets and specific gene expression are not well characterized in the renal tissues. Furthermore, kidney targeted drug delivery vehicles are not available [224,225].

Interventions of AKI tested in ovine models

Publications on the use of sheep models in kidney research, including testing therapies for AKI, are fewer compared to those using pigs but more than publications on the use of cats and dogs combined (Figure 1). One of the reasons is that sheep are an agricultural animal and easier to get approval for studies than cats and dogs. Therapeutics tested in the ovine models are listed in Table 3. The majority of publications are from May and colleagues from Australia.

Interventions of AKI tested in the feline and canine models

Studies of AKI in cats and dogs are significant in the field of veterinary medicine, but we limited our search to studies relevant for translational purposes. The search results are listed in Table 4. Cats and dogs are not widely used as models of translational AKI research because of ethical guidelines.

Conclusion

While they are the most commonly used animal models for AKI research, rats and mice have significantly different immune responses and anatomy compared to humans. This heterogeneity is one reason why promising therapeutics developed and tested in these animal models have failed to translate into clinical practice. In contrast, LAM have similarities to humans that may confer advantages when considering potential therapeutics for clinical studies. However, even large animals are not perfect replicas for human AKI. Further, animal experiments are planned in advance and carefully controlled, which is different from the clinical setting where AKI is multifactorial and patients have more variability

in terms of comorbidities, age, gender, and genetic diversity [226]. Despite these limitations, the knowledge gleaned from LAM studies has the potential to advance our understanding of the basic pathophysiologic mechanisms of AKI in higher-order animals and to serve as a bridge between murine models and clinical trials.

Disclosure statement

Authors declare no conflict of interest. The content and views expressed in this article are the sole responsibility of the authors and do not necessarily reflect the views or policies of the Department of Defense or US Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the Department of Defense or U.S. Government.

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