


REVIEW

Interorgan crosstalk mechanisms in disease: the case of acute kidney injury-induced remote lung injury

Andreas Herrlich 

Division of Nephrology, Department of Medicine, Washington University in St. Louis, MO, USA

***Correspondence**

Andreas Herrlich, Division of Nephrology,
 Department of Medicine, Washington
 University in St. Louis, Mail Stop Code
 MSC-8126-012-0863, 660 South Euclid
 Avenue, St. Louis, MO, USA
 Tel: 314 747 0565
 E-mail: aherrlich@wustl.edu

(Received 6 September 2021, revised 8
 December 2021, accepted 9 December
 2021, available online 4 March 2022)

doi:10.1002/1873-3468.14262

Edited by Stefan Rose-John

Homoeostasis and health of multicellular organisms with multiple organs depends on interorgan communication. Tissue injury in one organ disturbs this homoeostasis and can lead to disease in multiple organs, or multiorgan failure. Many routes of interorgan crosstalk during homoeostasis are relatively well known, but interorgan crosstalk in disease still lacks understanding. In particular, how tissue injury in one organ can drive injury at remote sites and trigger multiorgan failure with high mortality is poorly understood. As examples, acute kidney injury can trigger acute lung injury and cardiovascular dysfunction; pneumonia, sepsis or liver failure conversely can cause kidney failure; lung transplantation very frequently triggers acute kidney injury. Mechanistically, interorgan crosstalk after tissue injury could involve soluble mediators and their target receptors, cellular mediators, in particular immune cells, as well as newly identified neuro-immune connections. In this review, I will focus the discussion of deleterious interorgan crosstalk and its mechanistic concepts on one example, acute kidney injury-induced remote lung injury.

Keywords: acute kidney injury; acute lung injury; interorgan communication; multiorgan failure; remote inflammation; respiratory failure; secondary organ complications; systemic inflammation; tissue injury response

Homoeostasis in multicellular organisms with multiple organs and the response to its disturbance by injury are coordinated by cell–cell communication aimed at re-establishing and maintaining homoeostasis [1–3] on the organ, organ-to-organ or interorgan level. Studies of cellular functions in health and disease, to date, mostly focus on understanding cell–cell communication and its mediators within a given organ or diseased tissue [4]. Many physiological connections between organs, mediators and mechanisms that govern homoeostasis are known, but interorgan crosstalk during disease or disturbed homoeostasis is not yet well

understood. Clinical observations and animal experiments show that humans and mice respond to local tissue injury with disturbed systemic homoeostasis, which can trigger remote injury of the heart, lung, gut, brain, liver and of other organs [5–7]. As examples, acute kidney injury can trigger acute lung injury [8–10], cardiovascular dysfunction [11] or hepatic and intestinal dysfunction [12], while direct lung injury, for example, by infection, can cause kidney failure [13–16]. Lung transplantation very frequently triggers acute kidney injury and is very tightly correlated with the occurrence of primary graft dysfunction within the first

Abbreviations

AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CAP, cholinergic anti-inflammatory response syndrome; CARS, compensatory anti-inflammatory response syndrome; CKD, chronic kidney disease; DAMPs, damage-associated molecular patterns; FGF23, fibroblast growth factor 23; HMGB1, high mobility group protein 1; ICU, intensive care unit; NET, neutrophil extracellular traps; OPN, osteopontin; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor.

24–48 h after transplant, which, to a large degree, occurs due to ischaemic injury of the transplanted organ [17,18]. These observations suggest bidirectionality of interorgan crosstalk in disease, and they are underpinned by pre-existing interorgan communication mechanisms that are activated during disturbance of homeostasis and may, in part, represent adaptive responses. Yet, it is clear from the observed high mortality of multiorgan failure that these responses often have severely maladaptive consequences for the organism.

Mechanistically, interorgan crosstalk after tissue injury could involve soluble mediators and their target receptors, cellular mediators, in particular organ-resident or circulating immune cells, the nervous system, as well as newly identified neuro-immune connections [19,20]. Conceptually, it is useful to consider a timeline of steps that occur after tissue injury in a primary organ to understand the sequence of interorgan signals that may lead to secondary organ failure. First, tissue injury of any cause activates a cellular stress response with release of cytokines and diverse other molecules that activate the innate immune system. Depending on its severity, cell stress can lead to cell death, increased release of exosomes, of cell debris/fragments and of large quantities of DNA/RNA fragments, and the adenosine phosphates ATP and ADP. Together, this diverse group of molecules is termed ‘alarmins’, because they alarm the innate immune system. These molecules are not only locally increased at the site of primary tissue injury, but also can be found in the circulation [21–23]. Following the activation by alarmins, innate immune cells, such as neutrophils and monocytes, are attracted to the site of primary tissue injury. This requires temporary upregulation of adhesion molecules in endothelial cells and permissive endothelial permeability, to allow access of circulating soluble factors and immune cells to the site of tissue injury. Once in the tissue, monocytes can develop into different immune cell lineages, predominantly macrophages and dendritic cells [24,25]. But how does tissue injury and inflammation spread to a remote site? Since principally similar inflammatory events have been described at remote injury sites, a similar sequence of events as occurred at the primary tissue injury site might be postulated to occur at the remote site.

This review will discuss currently known interorgan crosstalk pathways using a clinically important example of interorgan crosstalk, namely, acute kidney injury (AKI)-induced remote acute lung injury (ALI) with respiratory failure, AKI-to-ALI or in short AKI–ALI used hereinafter [8–10].

Acute kidney injury is a common problem in the human population and develops in 2–5% of patients during hospitalization, in 50% of intensive care unit (ICU) patients, and in about 20% of kidney transplant patients within the first 6 months after transplantation [17,26]. Irrespective of its cause, AKI alone has a 15–30% mortality, which rises to 60–80% when AKI induces remote secondary organ complications (multi-organ failure), in particular AKI–ALI [8,10,26]. Traditional complications of AKI include electrolyte disturbances, metabolic acidosis and volume overload, which can be treated by dialysis. Independently, AKI causes non-traditional complications that cannot be corrected by dialysis (a concept first described here [27]), including remote injury of the lung (AKI–ALI), heart [28,29], liver and gut [30–32], brain [33] and also immune dysfunction with increased susceptibility to sepsis [34–36]. Although a number of AKI–ALI mediators have been described, much about their specific sources and lung target cells, as well as molecular mechanisms remains to be discovered. This review builds on and extends a number of excellent previous reviews of AKI–ALI [8,10,37–43]. For an expanded discussion on how AKI and ALI/ARDS interact, taking all clinically relevant physiological effects of AKI in particular reverse effects of ALI or its most severe form acute respiratory distress syndrome (ARDS) onto the kidney into account, the reader is referred to a recent excellent review [44]. Since publication of these reviews, newly recognized general interorgan crosstalk mechanisms and novel mediators of tissue injury-induced lung injury have been described. I will discuss these novel findings and provide a synopsis of AKI–ALI mediators, timelines for their release and action, their interactions, source and target cells and main mechanisms of action known to date (Fig. 1 and Table 1).

Mechanisms of acute lung injury after AKI

Circulating factors and the systemic inflammatory response syndrome

Data from patients with AKI show that kidney tissue injury induces a systemic inflammatory response syndrome (SIRS) with elevated levels of circulating cytokines, including, for example, the proinflammatory cytokines interleukin-6 (IL-6) [45–49], IL-8 [45,46,49–51] and tumor necrosis factor (TNF) [46]. SIRS can principally occur after a number of tissue injuries, often involving infection or sepsis [7], conditions frequently associated with AKI and ALI [13,14,35,52–

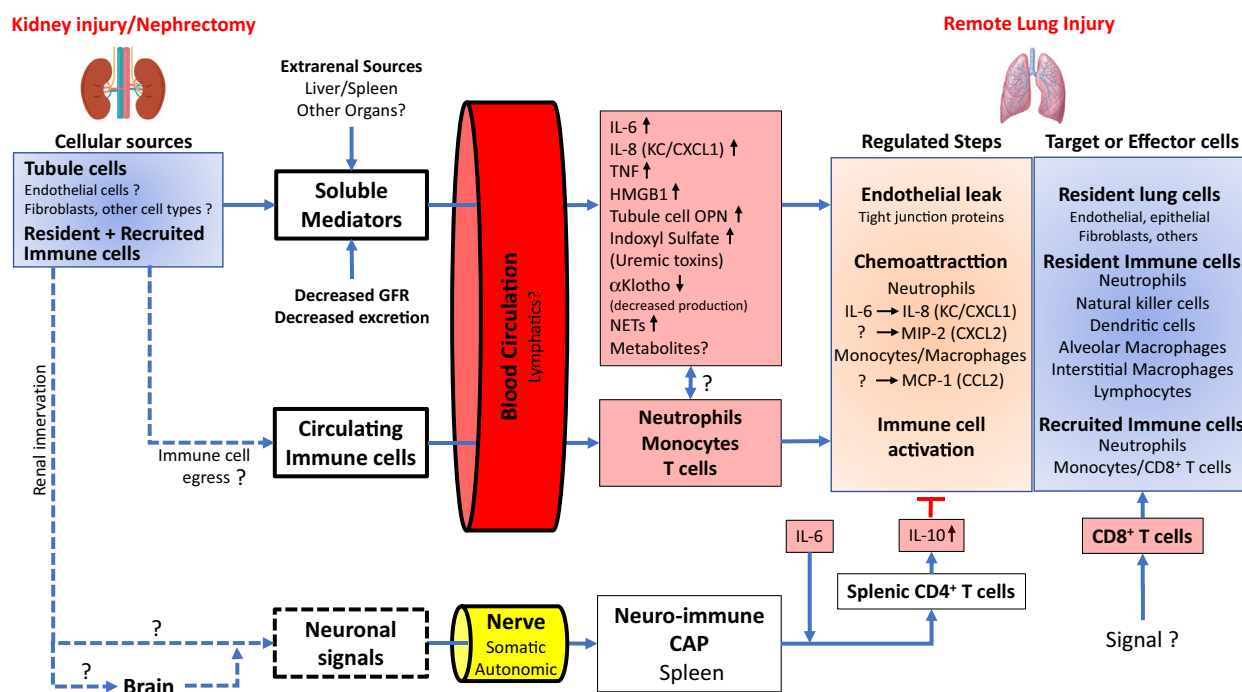


Fig. 1. Mediators of AKI–ALI. AKI–ALI is mediated by (a) soluble circulating factors, predicted to be released from the injured kidney or extrarenal sources affected by AKI or nephrectomy, (b) Circulating immune cells and (c) neuro-immune signalling, which is still in part speculative. Soluble circulating factors, such as interleukins (IL-6, -8, -10), TNF, the alarmin HMGB1, tubule cell-released OPN, the uraemic toxin Indoxyl sulphate, α Klotho and NET, as well as circulating immune cells address/affect one or several regulated steps that establish remote lung injury. It remains unclear whether soluble mediators act on circulating immune cells and/or lung resident/recruited immune cells and/or other lung-resident cell types (epithelial cells, fibroblasts, endothelial cells, others). Splenic CD4⁺T cells produce anti-inflammatory IL-10 in response to IL-6 stimulation or in response to vagal nerve stimulation, as part of the classical cholinergic anti-inflammatory pathway (CAP). Both represent negative feedback mechanisms that counter the SIRS. Whether metabolites produced by the injured kidney or other sources, including the lung itself, play roles in AKI–ALI is speculative. Decreased glomerular filtration rate and decreased excretion can elevate serum levels of cytokines after kidney injury. Decreased excretion of uraemic toxins, in particular indoxyl sulphate, could possibly also contribute to extrarenal production of the AKI–ALI mediator IL-6. α Klotho serum levels are decreased due to reduced production in the injured kidney. The signal that recruits CD8⁺ T cells into the AKI–ALI lung remains unknown.

55]. In principle, lung injury can also occur after ischaemic injury of other organs, for example, the liver, gut or hind limb [56–62], and this can involve some of the same circulating mediators as in kidney injury-induced ALI (AKI–ALI), suggesting that interorgan crosstalk between any injured organ and the lung potentially shares similar mechanisms.

Role of nephrectomy in cytokine upregulation

It has generally been assumed that circulating cytokines elevated after AKI are released into the circulation by the injured kidney. However, while this appears intuitive, this has not been shown conclusively for most known AKI–ALI mediators. Available data are predominantly based on kidney mRNA expression data but not, for example, kidney cell type-specific knockout of mediators. In fact, extrarenal sources of

elevated serum cytokines in AKI–ALI have been identified. In this context, experiments with bilateral nephrectomy (removal of both kidneys) provide interesting insights, since this procedure causes complete lack of glomerular filtration without the remote effects induced by mediators released from an injured kidney.

Interestingly, serum levels of a number of the AKI–ALI mediators discussed in this review, such as IL-6, have also been found upregulated after nephrectomy, indicating that there must be extrarenal sources of AKI–ALI mediators. Early studies comparing mice with bilateral nephrectomy or ischaemic AKI showed that both induced elevation of several serum cytokines, in particular, IL-6 and IL-1 β , with nephrectomy-induced elevations moderately lower than ischaemic AKI. Sham operation, where the kidneys are surgically exposed but not manipulated, also led to small elevations of cytokines, possibly due to stress of animal

Table 1. Synopsis of AKI–ALI mediators. Timelines for their release and action, their interactions, their source and target cells and main mechanisms of action known to date.

Interorgan crosstalk mediator	Baseline expression/ presence	Expression/ serum level after AKI	Expression/ serum level after nephrectomy	Approximate onset of serum elevation or decrease	Approximate peak of serum elevation or nadir of decrease	Approximate duration of serum elevation or decrease	Cellular source	Target cells	Endothelial leakage	Lung Neutrophil accumulation	Lung interstitial macrophage accumulation	Notes
Osteopontin	+	Upregulation	N.D.	0–2 h	12–24 h	> 5 days	Kidney only; distal and proximal tubule; later stages other kidney cell types	CD44 expressing circulating or lung immune cells and lung endothelial cells?	+++	+++	+++	
HMBG1	+	Upregulation	Upregulation	0–6 h	N.D.	> 1 day	Broadly expressed in kidney	Acts in part via TLR4 expressing immune cells	+	(+)	N.D.	
IL-6	(+)	Upregulation	Upregulation	1–2 h	2 h	6–12 h	Kidney, lung, liver, spleen, intestine	IL-6R/gp130 expressing cells	+	+++	N.D.	
KC/CXCL1 ('IL-8')	(+)	Upregulation	Upregulation	1–2 h	2 h	1 day	Lung endothelial cells	CXCR2 expressing cells	+	+++	N.D.	Induced by IL-6 together with other unknown AKI/ nephrectomy-induced co-factors
IL-10	(+)	Upregulation	Upregulation	4 h	8–24 h	> 1 day	Liver, splenic CD4 T cells	Immune cells?	Decrease by anti-inflammatory action	Decrease by anti-inflammatory action	N.D.	Induced by IL-6; Anti-inflammatory interleukin
TNF	(+)	Upregulation	Upregulation	1–2 h	2 h	1–2 days	Immune cells, macrophages	TNFR1 expressing lung endothelial cells; other cell types?	+	+++	N.D.	
Indoxyl sulphate (Uraemic toxin and inducer of IL-6)	+	Upregulation	Upregulation	0–2 h	Depends on severity of kidney failure and proximal tubule damage or loss	Until AKI-induced renal failure is resolved	Gut–liver-derived: Indole is produced by intestinal bacteria as a degradation product of the amino acid tryptophan, and is	Endothelial cells, vascular smooth muscle cells, epithelial cells, monocytes?	N.D.	N.D.	N.D.	Induces IL-6 expression

Table 1. (Continued).

Interorgan crosstalk mediator	Baseline expression/ presence	Expression/ serum level after AKI	Expression/ serum level after nephrectomy	Approximate onset of serum elevation or decrease		Approximate peak of serum elevation or nadir of decrease		Approximate duration of serum elevation or decrease		Cellular source	Target cells	Endothelial leakage	Lung Neutrophil accumulation	Lung interstitial macrophage accumulation	Notes
				serum elevation or decrease	serum elevation or decrease	serum elevation or decrease	serum elevation or decrease	serum elevation or decrease	serum elevation or decrease						
Klotho	+	Downregulation	N.D.	0–3 h	N.D.	7–10 days	subsequently metabolized in the liver to indoxyl sulphate	Kidney	FGF23/FGFR1 expressing cells?	+	N.D.				

manipulation, but at even lower levels than bilateral nephrectomy. Only ischaemic AKI and bilateral nephrectomy, but not sham operation, induced lung alveolar wall oedema and neutrophilic lung inflammation. Of note, bilateral nephrectomy or ischaemic AKI induced somewhat unique cytokine profiles, but also had significant overlap, suggesting at least some shared mechanisms [63]. A follow-up study of the same group showed that bilateral nephrectomy-induced AKI–ALI depends on IL-6. IL-6^{−/−} mice or IL-6 neutralizing antibody reduced lung myeloperoxidase activity (MPO, a biochemical marker for tissue neutrophil content), lung KC/CXCL1 (the mouse homologue of human IL-8) protein expression, lung interstitial oedema and capillary leak (as measured by Evans Blue extravasation) and neutrophil infiltration by 30–50% after bilateral nephrectomy [64]. It was later shown that the IL-6-induced AKI–ALI mediator KC/CXCL1 (‘IL8’) is produced by lung endothelium after bilateral nephrectomy [65]. Another bilateral nephrectomy study showed that inhibition of a neutrophil enzyme, neutrophil elastase, moderately blunts the effects of nephrectomy on the lung [66]. Another early study found that only ischaemic AKI, but not bilateral nephrectomy, caused increased lung endothelial barrier permeability and inflammation. However, when assessed on the gene expression level (microarray), some lung gene expression changes could also be detected at 36 h after bilateral nephrectomy and only partially overlapped with those induced by ischaemic AKI. It is possible that in this particular study, bilateral nephrectomy caused less AKI–ALI mediator upregulation, but serum IL-6 or other mediators were not determined [67]. In a very recent study in mice, nephrectomy did not produce significant changes in lung alveolar wall oedema or accumulation of lung immune cells. Also, in this study, IL-6 or other cytokine levels were not determined in detail after nephrectomy [68]. The reasons for these discrepancies are not clear, but it is theoretically possible that even though inbred C57Bl6 mice were used in most of these studies, drift in their genetic background may occur over time and could play a role, or differences in surgical technique or anaesthetic protocols used.

Extrarenal cytokine sources

Extrarenal sources of AKI–ALI mediators after bilateral nephrectomy or AKI likely include the liver and spleen, which, for example, show IL-6, IL-10 or TNF mRNA and/or protein upregulation [12,69]. However, mRNA or protein upregulation of a given AKI–ALI mediator in a given organ does not necessarily prove

that this organ releases this mediator into the circulation. Immune cells, in particular monocytes or macrophages, may also represent secondary sources of AKI–ALI mediators beyond the kidney. Depletion of mononuclear phagocytes by intravenous injection of liposomal clodronate reduced serum cytokine elevations (including IL-6, KC/CXCL1, IL-10, IL-1 β , IL-5, MCP-1 and eotaxin) after bilateral nephrectomy, suggesting that circulating monocytes and their tissue macrophage progeny contribute to serum cytokine elevations after nephrectomy [69], and very likely also after AKI, where immune cells at the primary (kidney) and secondary remote injury site (lung) might be involved. This could involve cytokine production by monocytes or macrophages directly and/or occur indirectly by induction of cytokine expression in nonimmune cells driven by monocytes or macrophages. In another example of a secondary cytokine source, mice with AKI upregulated production of the anti-inflammatory IL-10 in the spleen, resulting in elevated IL-10 serum levels, which limited AKI-induced lung injury [70]. Serum IL-10 has also been found upregulated in the serum and spleen after nephrectomy [63,69].

Role of uraemia in cytokine upregulation

AKI–ALI after bilateral nephrectomy or acute kidney injury could, in part, occur because of decreased glomerular filtration rate, leading to a reduction in the excretion of molecules, including of inflammatory molecules or cytokines themselves, as well as of uraemic toxins. Decreased renal clearance of cytokines, such as IL-6, is indeed partially responsible for an increase in serum cytokine levels [69]. What signals drive extrarenal production of cytokines in response to nephrectomy or AKI, however, is not yet well defined. More recent evidence points to a potential role of uraemic toxins in this process (reviewed in Ref. [71,72]). Indole is produced by intestinal bacteria as a degradation product of the amino acid tryptophan and is subsequently metabolized in the liver to indoxyl sulphate. Indoxyl sulphate, an organic anion, is a small protein-bound uraemic toxin that is normally actively secreted into the urine driven by basolateral organic anion transporters in renal proximal tubule cells [73]. Proximal tubules are a key cell type injured by AKI and lost in chronic kidney disease (CKD), and thus indoxyl sulphate excretion is reduced and its serum levels are elevated in both conditions. Mounting evidence suggests that indoxyl sulphate is also a signalling molecule and can induce the expression of IL-6 in endothelial, smooth muscle cells, proximal tubule cells or a

monocyte-derived cell line, involving the intracellular aryl hydrocarbon receptor and NF κ B pathway activation [74–76]. These findings provide a possible direct connection between uraemia and upregulation of the AKI–ALI mediator IL-6 after nephrectomy from extrarenal sources or after AKI from both intrarenal and extrarenal sources. Another mechanism by which uraemic toxins can contribute to noncardiogenic pulmonary oedema is by accumulation in the lung and pleural fluid. Here, they influence salt and water transport by dysregulating sodium and water clearance *via* downregulated expression of epithelial sodium channels, the Na, K-ATPase and aquaporin water channels 1 and 5 [77–80].

Further complicating the interpretation of elevated cytokines in nephrectomy or AKI-induced ALI is the fact that some murine AKI–ALI mediators studied, to date, are not only found upregulated in the injured kidney, other organs or the circulation, but also in the remotely injured lung; we will discuss examples of this in the following. As a consequence, when using mediator inhibitors or global gene knockout strategies of a given mediator, it is difficult to determine whether the observed effects can be attributed to blocked action of kidney-expressed, secondary organ-expressed, circulating or lung-expressed mediator, or their combination.

Interleukins: IL6, IL8, IL10

Early studies in the field reported the involvement of interleukins in AKI–ALI and identified IL-6 and IL-8 (KC/CXCL1 in mice) as AKI–ALI mediators. IL-6 and IL8 serum elevations already 2 h after AKI predict prolonged need for mechanical ventilation in children after cardiac surgery [45], a finding that has been interpreted as the occurrence of AKI–ALI in humans. Both IL-6 and IL-8 are elevated in the serum and bronchoalveolar lavage of patients with ALI and predict their mortality [81,82]. IL-8 is elevated in the serum of AKI patients and predicts their mortality [46]. A multitude of studies links IL-8 to the pathology of ALI in humans [54,81–83]. Taken together, these findings suggest that IL-6 and IL-8 might, indeed, have roles in AKI–ALI in humans.

In mice, kidney IL-6 mRNA is upregulated after nephrotoxic or ischaemic AKI [84–86]. Serum IL-6 protein is elevated within 1–2 h after ischaemic AKI in mice, peaks at 2 h and returns to baseline within 6–12 h [63,64]. IL6 global knockout or IL-6 neutralizing antibody treatment in mice prevents AKI-induced lung neutrophil recruitment, but only moderately reduces vascular leakage [64]. This predicts the existence of other factors that regulate lung endothelial leakage

after AKI that likely act upstream or in parallel to IL-6. Serum KC/CXCL1 (the mouse homologue of human IL-8) protein is elevated within 1–2 h after ischaemic AKI in mice, peaks at 2 h and returns to baseline within 12–24 h, roughly mirroring IL-6 elevations [63]. Other factors appear to act in parallel with IL-6 in the induction of neutrophil chemoattractant expression in the lung after AKI. Only AKI-induced lung expression of the chemokine KC/CXCL1 ('IL-8') was blocked by IL-6 neutralization after AKI, but not lung CXCL2/MIP2 expression, suggesting that IL-6 acts upstream of lung KC/CXCL1 ('IL-8') but not of lung CXCL2/MIP2, which may be induced by other kidney injury-released AKI–ALI mediators. IL-6 injection into uninjured mice caused neutrophil accumulation in the lung but did not induce KC/CXCL1 or CXCL2/MIP2 [64], indicating that IL-6 action occurs in concert with other injury-induced neutrophil attractant mechanisms. Injection of IL-6 into IL-6 KO mice with AKI reversed their protection from AKI–ALI and induced lung endothelial KC/CXCL1 ('IL-8'). KC/CXCL1 ('IL-8') neutralizing antibody or global knockout of the KC/CXCL1 receptor CXCR2 reduced lung neutrophil accumulation, but only moderately reduced lung vascular leakage [65], similar to IL-6 inhibition and consistent with its predicted role upstream of KC/CXCL1 ('IL-8') [64]. Endothelial-specific knockout of KC/CXCL1 ('IL-8') was not examined in this study.

Beyond the kidney, liver or spleen, IL-6 has also been found upregulated in the remotely injured lung after AKI. Lung IL-6 mRNA expression was elevated 2 h after AKI at much lower levels than the kidney, but lung IL-6 protein levels were not, at least not at this early time point [65]. IL-6 protein was also not upregulated in lung bronchoalveolar lavage fluid 4 h after AKI [87]. However, in a bilateral nephrectomy study, IL-6 is significantly upregulated in the remotely injured lung at 6 and 24 h after nephrectomy [66]. Yet, based on the observed lung IL-6 mRNA upregulation early after AKI, lung produced IL-6 protein may have a role in a later phase of AKI–ALI.

Taken together, these results can be interpreted to indicate that circulating IL-6 is not a major regulator of endothelial leakage, which requires yet unknown co-factors. IL-6, however, induces neutrophil attraction to the lung that at least, in part, depends on lung endothelial KC/CXCL1 ('IL-8'). Thus, IL-6 acts upstream of lung endothelial KC/CXCL1 ('IL-8'). Specific source cells of IL-6 likely include the kidney, liver and spleen, but specific target cells in the lung or circulation remain unknown to date. Of note, IL-6 can also have anti-inflammatory effects and it is important

where in the lung IL-6 acts. Intratracheally instilled IL-6 as compared to intravenous injection did not worsen AKI–ALI, but rather had an anti-inflammatory effect [87].

IL-10 is an anti-inflammatory cytokine and part of the compensatory anti-inflammatory response syndrome (CARS) that counteracts SIRS after tissue injury, including of the kidney [46]. One part of this response, the cholinergic anti-inflammatory pathway (CAP), is transmitted by the vagus nerve, with afferent fibres sensing peripheral inflammation and efferent fibres, including the splenic nerve, inducing anti-inflammatory signals, such as IL-10 and reducing inflammatory cytokine release, such as TNF, by influencing the biology and activity of splenic immune cells [88]. Serum IL-10 is elevated after AKI in mice and humans [46,86]. The dominant source of IL-10 in this context appears to be immune cells in the spleen, in particular CD4⁺ T cells. IL-10 was strongly upregulated in the spleen 4 h after AKI in mice, and to a much smaller degree in the liver. Splenectomy reduced IL-10 after AKI and worsened AKI–ALI with increased capillary leak and increased lung neutrophil invasion (lung MPO activity). Serum IL-6 elevations and lung KC/CXCL1 ('IL-8') were strongly enhanced after AKI with splenectomy as compared to AKI alone, but not the expression of kidney or liver IL-6, suggesting that there are additional sources that elevate serum IL-6 after kidney injury. IL-10 administration after AKI in splenectomized mice limited serum IL-6 elevations, lung KC/CXCL1 ('IL-8') expression and lung neutrophil invasion (lung MPO activity) [86], highlighting the fact that the anti-inflammatory IL-10 dampens pro-inflammatory IL-6 production in a negative feedback mechanism and thereby reduces lung injury. Consistent with these results, IL-10 green fluorescent reporter mice showed IL-10 upregulation after AKI only in the spleen, but not in the liver, lung or kidney. IL-10 knockout mice showed the same kidney injury at 4 h after AKI as compared to *wt* mice, but enhanced AKI–ALI with increased lung KC/CXCL1 ('IL-8') and lung neutrophils (lung MPO activity). IL-6-deficient mice also showed regular kidney injury as compared to *wt* mice, but lacked IL-10 upregulation after AKI, suggesting again that IL-6 acts upstream of splenic IL-10. *In vitro* experiments indeed showed that IL-6 stimulation increased IL-10 production in splenic CD4 T cells, B cells and macrophages. In line with these findings, CD4 knockout mice showed reduced splenic IL-10 upregulation after AKI and worsened AKI–ALI [70].

Collectively, studies on interleukins, thus, suggest that IL-6 acts upstream of splenic IL-10 production and lung KC/CXCL1 ('IL-8') *in vivo* and that splenic

CD4⁺ T-cells represent an important source of IL-10 after AKI. IL-10, in turn, reduces IL-6 and lung KC/CXCL1 ('IL-8') in a negative feedback loop. IL-6 is likely released from the kidney and extrarenal organs, KC/CXCL1 ('IL-8') from lung endothelial cells and IL-10 from the spleen and liver, but lung or immune target cells of IL-6, KC/CXCL1 ('IL-8') or IL-10 still need to be better defined.

Tumor necrosis factor and its receptor TNFR1

An early study showed that AKI induces apoptosis of lung cells at 24 h after AKI, most likely of CD34-positive lung endothelial cells, as detected by TUNEL stains and caspase-3 activation. Gene expression analysis of apoptosis related genes in the lung after AKI identified many genes related to the TNF pathway (formerly called TNF-alpha, a key type 1 cytokine), suggesting that soluble TNF and its main receptor TNFR1 mediate lung cellular apoptosis in AKI–ALI [89,90]. Consistent with this, TNFR1 global knockout mice did not show lung cell apoptosis after AKI [91]. Serum TNF is elevated after AKI within 1–2 h, with a peak at 2 h and elevated levels lasting for 1–2 days [29]. TNF expression is induced during AKI predominantly in macrophages and in T cells. Kidney nonimmune cells express comparably little TNF [92]. TNF was also upregulated in the liver after bilateral nephrectomy or AKI, indicating that other extrarenal sources exist [12]. Serum TNF in this particular study was found elevated at 2–4 h after AKI but not at 24 h. In comparison, lung TNF mRNA and protein were not upregulated at these time points, suggesting that the kidney but not the lung represented a source of TNF in AKI–ALI [90]. However, in a bilateral nephrectomy study, TNF was found significantly upregulated in the remotely injured lung at 6 and 24 h after nephrectomy [66]. These discrepancies might be observed because of differences in the extent of immune cell infiltration in the lung, given that immune cells are known significant sources of TNF. In contrast to TNF, its receptor TNFR1 showed significant upregulation in the lung 4 and 24 h after AKI [91], consistent with increased TNF pathway activation in the lung induced by AKI. TNF inhibition with the TNF scavenger etanercept (TNFR2-Fc) strongly reduced pulmonary apoptosis at 24 h after AKI, as well as bronchoalveolar protein accumulation, a surrogate of endothelial leak [91]. The effects of TNF inhibition at earlier time points after AKI were not assessed. One related study of the effects of etanercept on the induction of ALI in a sepsis/SIRS model [induced by repeated intraperitoneal injection of lipopolysaccharide

(LPS)] suggested that when TNF inhibition was started prior to induction of sepsis/SIRS, the development of ALI was prevented, but not when started at 2 h after induction of sepsis/SIRS, pointing at potential early effects of TNF in the induction of remote lung injury [52]. TNFR1 endothelial cell-specific knockout has not been tested in AKI–ALI. Thus, whether lung endothelial cells alone and/or other cells present in the lung represent target cells of circulating TNF still requires further investigation.

High mobility group protein 1

Damage-associated molecular patterns (DAMPs) belong to the larger group of 'alarmins' and function as endogenous danger molecules released from damaged or dying cells which activate the innate immune system (PAMPs are their pathogen-associated counterparts). Although they contribute to the host's defence, they can also promote pathological inflammatory responses. High mobility group protein 1 (HMGB1) is one such DAMP/'alarmin', and its serum concentrations are highly elevated after bilateral nephrectomy. Mice with a spontaneous mutation that impairs Toll-like-receptor 4 (TLR4) signalling (C3H/HeJ mice), a receptor for HMGB1, showed HMGB1 serum elevations 6 h after nephrectomy comparable to *wt* mice (C3H/HeN). Yet, TLR4 mutant mice showed mild to moderately reduced lung mRNA expression of KC/CXCL1 ('IL-8'), IL-6 and of TNF, as well as moderately reduced endothelial leakage and very mildly reduced lung neutrophils as compared to *wt* controls. This relative protection could be mimicked with injection of a neutralizing antibody to HMGB1 into *wt* controls, whereas protection could be reversed by transfer of *wt* immune cells (splenocytes) into TLR4 mutant mice, indicating that it was TLR4 expression in immune cells that was responsible [93]. HMGB1 is broadly expressed, but the exact cellular sources of HMGB1 in the kidney or elsewhere and its specific target cells have not been determined to date. Of note, serum HMGB1 is also elevated in mice with ischaemic AKI [94], and in AKI patients [95], but whether it has a role in human AKI–ALI remains unknown.

Osteopontin

Osteopontin (OPN/SPP1) represents the most recently identified mediator of AKI–ALI. OPN, initially identified as a regulator of bone biomineralization and remodelling, is a secreted immunoregulatory molecule expressed in a variety of cells, including stromal, epithelial and immune cells [96–100]. OPN is strongly

chemotactic for immune cells, in particular for neutrophils and macrophages, and enhances Th1 inflammation [101–103]. Serum OPN protein levels have been studied as a biomarker of severity of disease in patients with multiorgan failure, often including AKI and ALI [104,105].

Lung injury in mice and likely also in humans occurs within 1–2 h after AKI. This indicates that some responsible mediators must be released very early and are potentially already expressed in the kidney during homeostasis, to enable quick release upon stress. OPN, similar to HMGB1, appears to represent such a mediator; in contrast to, for example, IL-6, IL-8 or TNF which are hardly expressed in the normal kidney and require upregulation by injury. A recent study that applied single-cell RNA sequencing (scRNAseq) for the first time to AKI–ALI identified OPN released from the injured kidney after ischaemic AKI as a key mediator of lung endothelial leakage and inflammation in AKI–ALI [68]. Using kidney and lung scRNAseq after AKI or sham operation in mice (24 h after operation) followed by computational ligand–receptor pairing analysis across organs, kidney ligands to cognate lung receptors, kidney osteopontin was predicted to act as an AKI–ALI mediator and interact with CD44 receptors in lung cells. Based on scRNAseq, OPN was significantly expressed in distal and to a lower degree proximal tubule at baseline, suggesting the possibility of quick release after injury. At 24 h after injury, OPN was significantly upregulated in distal and proximal tubule and in numerous other kidney cell types, including immune cells. Based on qPCR measurements in kidney and lung tissue lysates, OPN mRNA was indeed upregulated already at 2 h after AKI, peaked at 12 h and remained elevated until at least Day 5 after injury. OPN mRNA in the lung was barely upregulated over the same time frame studied, suggesting that the kidney might represent an important source of OPN in AKI–ALI, but not the lung. OPN serum levels were measurably upregulated within 1–2 h and significantly by 4 h, and generally followed the pattern of OPN mRNA expression in the kidney. OPN neutralizing antibody injected at reperfusion or genetic OPN inhibition (OPN-global-KO mice) did not interfere with kidney injury, but almost completely prevented lung endothelial leakage (Evans blue extravasation, electron microscopy of lung endothelial cells), lung neutrophil and interstitial macrophage accumulation (immunofluorescence and/or mass cytometry) and respiratory failure with decreased oxygenation (blood gas measurements). Lung endothelial tight/adherens junction proteins, in particular of zonula occludens-1 (ZO-1), were downregulated and

electron microscopic evaluation showed reduced lung endothelial tight junction length on Day 1 after AKI, but not sham operation. Taken together, this suggests that OPN represents a key regulator of AKI-induced lung endothelial leakage and inflammation. OPN's relationship to other AKI–ALI mediators that moderately influence endothelial leakage, such as IL-6 or TNF, was not examined.

In order to determine the source of OPN, the investigators used functional kidney transplantation in mice. Transplantation of ischaemic *wt* kidneys raised OPN serum levels in the recipient mouse and caused AKI–ALI, but not transplantation of ischaemic OPN-global-knockout kidneys, identifying kidney-released OPN as necessary interorgan signal to cause AKI–ALI (transplanted *wt* or OPN-global-KO kidneys showed equal injury). This experiment shows for the first time conclusively that an AKI–ALI mediator is indeed released from the injured kidney and indicate that in the case of OPN extrarenal sources do not significantly contribute to OPN serum levels. Transplantation of a *wt* kidney into OPN-global-KO mice raised OPN serum levels and reversed their protection from AKI–ALI. However, OPN was not sufficient to induce AKI–ALI by itself. OPN injection into uninjured mice did not yield AKI–ALI, but rather required the presence of AKI. In the context of mild AKI at a level that did not induce overt AKI–ALI at 6 h after reperfusion, OPN injection yielded severe AKI–ALI as was observed after severe AKI. These results clearly indicate that other AKI–ALI mediators are still needed for OPN to act. Interestingly, exogenous fluorescently marked OPN injected into a *wt* mouse or endogenous OPN released from a *wt* kidney transplanted into an OPN-global-KO mouse was detectable in the lung and colocalized with alveolar and interstitial macrophages highly expressing CD44. These results predict a potential role of these immune cells as targets of OPN in the lung. Finally, OPN serum levels in mice were strongly positively correlated with severity of kidney injury [68].

An earlier study in rats also evaluated the effect of ischaemic AKI induced by kidney transplantation on lung injury. In this study, transplantation of ischaemic renal grafts into rats caused AKI–ALI. Osteopontin protein was upregulated at low levels in serum and also moderately in lung tissue, but the cellular source of osteopontin, and whether OPN was upregulated in and released from the injured transplant kidney, was not assessed. Systemic downregulation of OPN by hydrodynamic siRNA injection improved lung injury after kidney transplantation [106]. One study in mice connected OPN to lung injury after intestinal ischaemia. OPN was found upregulated at relatively low levels in both the

ischaemic gut and the remotely injured lung, not allowing to identify the source of serum OPN elevations. OPN neutralization significantly improved gut injury, but only mildly improved lung injury [58], suggesting that OPN does not represent a major causal link in gut injury-induced lung injury. Interestingly, the uraemic toxin indoxyl sulphate is able to induce OPN upregulation in vascular smooth muscle cells *in vitro* [107] and *in vivo* in aortic calcifications [108]. This allows the possibility that uraemia might also be involved in the upregulation of kidney OPN.

In human serum samples, OPN was strongly elevated in AKI patients but not in chronic kidney disease (CKD) patients and correlated with kidney injury [68]. A study in ICU patients reported as primary outcome that persistently elevated OPN serum levels correlate with increased mortality in multiorgan failure. The same study also suggested in secondary analysis that OPN serum levels are correlated to increased need of ventilation [109]. Another study of critically ill patients with multiorgan failure including AKI requiring dialysis found that OPN levels in this cohort were significantly elevated when compared with critically ill controls without AKI [110]. Taking these data together, it, thus, appears possible that OPN may also play a role in human AKI–ALI.

While clinically AKI-induced ALI is likely underrecognized due to many confounders, such as co-existing hypervolemia or cardiac dysfunction, which often serve as primary explanations for respiratory distress in AKI patients, it is very much clinically recognized that ARDS is significantly negatively affected by the presence of AKI [111] (reviewed in Ref. [44]). In this context, it is interesting to note that alveolar macrophages in ARDS patients highly express OPN [112,113], and lung macrophages also expressed OPN in an experimental mouse model of ALI/ARDS [112]. Additionally, increased OPN levels in sputum or bronchoalveolar lavage have also been linked to inflammation and severity of disease in other human lung diseases, such as cystic fibrosis [114], chronic obstructive pulmonary disease [115] and asthma [116]. Kidney injury-released OPN may, thus, represent an important modifier of existing lung disease, such as ALI/ARDS.

α Klotho

α Klotho is a molecule predominantly produced and released by the kidney under normal physiological conditions that function as an obligate co-receptor for fibroblast growth factor 23 (FGF23), a molecule that is crucial for mineral metabolism [117]. Mice deficient in α Klotho were found to develop multiorgan failure

similar to ageing [118], an initial indication of α Klotho's possible function in interorgan crosstalk. Several investigations have shown that α Klotho does not only affect mineral metabolism, but also acts as an inhibitor of apoptosis, fibrosis and cell senescence, and as an up-regulator of autophagy [119–122], effects that could mechanistically link a reduction in circulating α Klotho to multiorgan dysfunction. AKI leads to reduced expression of α Klotho mRNA in the kidney of rats and mice and reduced α Klotho serum and urine levels in mice, already detectable 3 h after AKI [119,123], and lasting for 7–10 days. Available data suggest that this likely also occurs in human AKI (reviewed in [117]). This allows for the possibility that α Klotho deficiency could contribute effects during the induction phase of AKI-induced remote organ injuries, as well as maintenance of such injuries beyond the initial phase. Exogenous replacement of α Klotho 6 h after AKI reduced lung oedema, increased lung antioxidant capacity and decreased lung oxidative DNA injury assessed at Day 3 after AKI [124]; earlier time points of α Klotho repletion were not assessed. In summary, based on available data to date, α Klotho represents one example of a kidney-released molecule that regulates systemic organ homeostasis at baseline. Its deficiency contributes to acute lung injury after AKI. The mineral metabolism actions of FGF23 are carried out *via* the ubiquitously expressed FGFR1 [125,126], in conjunction with its co-receptor α Klotho [127]. Whether the nonmineral effects of FGF23/Klotho in AKI–ALI are also mediated *via* FGFR1 remains unknown.

Immune cells

Neutrophils

There is ample evidence that neutrophils play a part in AKI–ALI, based on multiple studies that report their accumulation in the lung after AKI (reviewed in Ref. [8]). They appear to have a role in early AKI–ALI, as they invade the lung already 1–2 h after AKI [68,128]. However, no study, to date, has assessed the effect of neutrophil depletion on AKI–ALI. It remains unknown whether neutrophils represent primary players that directly receive signals from interorgan cross-talk mediators to initiate AKI–ALI, or whether they are part of the general inflammatory machinery set in motion downstream of such mediator signals.

Monocytes/macrophages

An increase in monocytic cells and interstitial macrophages has been identified in the lung of humans and

rodents after AKI [129–132], but their mechanistic role, ontogeny (resident vs. recruited from the circulation) and whether they are primary receivers of interorgan crosstalk signals has not been determined. One study attempted to assess the role of monocytes and interstitial macrophages in AKI–ALI by diphtheria toxin elimination (CD11b-DTR mice). Results were difficult to interpret because diphtheria toxin, as applied in this model in the setting of AKI, already caused pro-inflammatory changes in mice, confounding interpretation. However, relative depletion of alveolar macrophages with intratracheal liposomal clodronate (LEC) moderately reduced lung KC/CXCL1 ('IL-8') protein expression and lung neutrophils (lung MPO activity), but increased lung capillary leak. Increased capillary leak was also observed with monocyte/macrophage depletion by diphtheria toxin [131]. Thus, based on this somewhat limited study, monocytes and interstitial or alveolar macrophages may have injurious but also some protective roles in AKI–ALI, such as in respect to protection of capillary integrity. A recent study documented the accumulation of interstitial macrophages in the remotely injured mouse lung after AKI–ALI starting already at 1 h and lasting at least until Day 5 after injury and identified them as potential target cells of OPN [68].

T cells

The strongest evidence for a mechanistic role of immune cells in AKI–ALI is available for T cells. The role of splenic CD4⁺ T cells in limiting AKI–ALI *via* production of the anti-inflammatory cytokine IL-10 early after AKI (4 h) [86] was discussed earlier. Within 24 h after AKI predominantly CD8⁺ T cells invade the lung and show signs of T-cell activation; however, such T-cell activation cannot be detected at 4 h after AKI. T-cell-deficient nude mice (T_{nu/nu}) showed AKI like *wt* mice based on serum creatinine 24 h after injury but showed reduced lung cell apoptosis (caspase-3-positive cells on lung immunohistochemistry) and lung capillary leak [bronchoalveolar lavage (BAL) fluid analysis]; other features of AKI–ALI were not assessed. Adoptive transfer of T cells into T-cell-deficient mice (T_{nu/nu}) reversed this protection [133]. These findings suggest that CD8⁺ T cells have roles at later stages of AKI–ALI but possibly not in the early initiation phase. What interorgan signals these T cells receive and through which receptors, where they come from, how they home to the lung and how they act, remains unknown.

Neutrophil extracellular trap formation

Neutrophil extracellular traps (NETs) are large, extracellular, web-like structures composed of cytosolic and granule proteins assembled on a scaffold of decondensed chromatin released from neutrophils in a form of cell death called NETosis. NETs trap, neutralize and kill bacteria, fungi, viruses and parasites, but are progressively also recognized as contributing to the pathogenesis of diseases unrelated to infection (reviewed in Refs [134,135]). NETs are found in the injured kidney but also in the circulation and lung after AKI, and citrullinated histones are an important component and also stimulant of NET formation. NET formation depends on peptidyl arginine deiminase (PAD) enzymes that convert arginine residues of histones to citrulline [136], resulting in chromatin decondensation and NET release. In a study in mice, NETs were detected in the kidney and lung 24 h after ischaemic AKI, while circulating NETs and circulating citrullinated histones were already detected in plasma 15–24 h after kidney injury. A PAD inhibitor or anti-histone antibody ameliorated kidney and lung injury and NET formation after AKI [137]. These results suggest that NETs may have a role in AKI–ALI, but whether it is circulating NETs and citrullinated histones that act as interorgan mediator to seed NET formation in the lung, or whether NET formation in the lung occurs predominantly after another interorgan mediator induces neutrophil ingress into the lung followed by NETosis remains unknown and will require further study.

Metabolites

Recent data suggest that AKI induces metabolic alterations, for example, in the heart [138] or lung [139,140], possibly implicating metabolites in AKI–ALI. In mice subjected to bilateral ischaemia reperfusion injury, the metabolome of the remotely injured lung was examined by mass spectrometry 4 h after bilateral kidney ischaemia reperfusion injury and compared to sham operation. Fatty acid oxidation (FAO) was the most significantly upregulated metabolic pathway in the lung after AKI, which could in principle have resulted from mitochondrial dysfunction in the lung and/or the kidney, as FAO was also upregulated in the injured kidney. The glycolytic pathway was the only significantly downregulated pathway in the AKI–ALI lung [139]. Mitochondrial dysfunction was previously shown to lead to the release of mitochondrial damage-associated patterns (mtDAMPs), which, in turn, were shown to be able to cause remote lung

injury [141,142]. Plasma and bronchoalveolar lavage mitochondrial DAMPs were, indeed, elevated after AKI but not sham operation, and mtDAMPs isolated from injured kidneys and injected into mice caused similar but not completely overlapping changes of the lung metabolome, with FAO also strongly affected [139], suggesting that mtDAMPs possibly released from the kidney could act on the lung. Another study also assessed the lung metabolome at 4 h, 24 h and 7 days after ischaemic AKI or sham operation. Measurements of lung inflammation, lung MPO activity and lung KC/CXCL1 ('IL8') expression were elevated and peaked at 4 h after AKI, and lung ATP depletion had a nadir at 4 h. Lung ATP is to 80% produced by mitochondrial respiration (oxidative phosphorylation) and its depletion reports oxygen poor states and/or mitochondrial dysfunction. The most significant changes in the metabolome were detected at 24 h. Beyond ATP depletion, the analysis revealed evidence of alternative energy production and increased oxidative stress in the lung [140]. Whether the observed metabolic changes and/or altered metabolites act as AKI–ALI mediators and have a direct role in establishing or driving AKI–ALI or whether they are a result of interorgan crosstalk driven by other AKI–ALI mediators that signal between the kidney or extrarenal organs and the lung is unresolved to date.

Neuro-immune connections

A significant interplay between neurons of the peripheral or autonomous nervous system and the immune system in health and disease has been recognized in recent years [143,144], but while its involvement in AKI–ALI seems likely, this still remains speculation. The kidney is densely innervated by sympathetic efferent nerves originating from the brain, and by sensory afferent nerves that transmit various signals from the kidney back to the brain [145]. Primary and secondary lymphoid organs, and here in particular the spleen, have intricate innervation by sympathetic and peptidergic nerves [146–149]. It has become well accepted that immune cells modulate signals and function of afferent sensory neurons, and that both afferent and efferent autonomic neurons, in turn, modulate the biology of associated immune cells and organ function. As an example, immune cells respond to DAMPs and PAMPs with production of cytokines and peptidergic inflammatory mediators. Receptors for these molecules are also present in neurons, which sense their presence and, as a result, transmit signals to the CNS [143]. Release of neuropeptides and transmitters by neurons, conversely, stimulates receptors on immune cells and

endothelial cells that reside in the same anatomical niche, and influences their biology [150–152]. Molecules released in the normal or injured kidney could, thus, act on kidney neurons and affect lung biology without having to reach the lung *via* the circulation. Since the nervous system, and in particular the autonomic nervous system, connects all organ systems to the CNS, it is, thus, likely that inflammatory or anti-inflammatory reactions in remote organs are influenced by neuro-immune interactions. Such interactions would allow to transmit signals from sites of primary tissue injury, such as the kidney, to secondary remote organs, such as the lung, and would also allow feedback communication from the lung back to the kidney.

Direct evidence for neuro-immune interactions is currently limited for AKI–ALI. However, indirect evidence suggests neuro-immune connections in AKI–ALI. Results obtained after AKI in the context of splenectomy cannot only be explained by removal of splenic immune cells, but rather also by removal of the autonomic anti-inflammatory input into splenic immune cells, since splenic nerve connections are severed during splenectomy. Mice with AKI and splenectomy showed significantly worsened AKI–ALI as compared to controls, mediated largely by a decrease in the production of anti-inflammatory IL-10 by CD4⁺ T cells in the spleen [70,86]. Vagus nerve stimulation has, indeed, been shown to have anti-inflammatory effects in a number of different organ injury models [153,154]. Central vagus nerve stimulation prior to kidney injury protects against the development of AKI and this effect depends on cholinergic signalling to splenocytes *via* $\alpha 7nAChR$ receptor [155]. Selective stimulation of efferent or afferent vagal nerve fibres has the same protective anti-inflammatory effect after AKI [156]. How and whether direct vagus nerve stimulation affects AKI–ALI remains, however, unknown to date.

Future directions and open questions

In order to target AKI–ALI therapeutically, several challenges remain. Beyond neutralizing the mediators in the circulation, it may be possible to attack AKI–ALI on various other levels, including, for example, the blockade of mediator upregulation, of mediator interaction with their target receptors or of responses that these mediators induce in their respective target cells. Prevention of the initiation of AKI–ALI would be the best strategy, but therapeutic efforts could also centre on blocking factors that maintain AKI–ALI in order to hasten resolution. Research efforts in the

future will, thus, need to focus in greater detail on cellular sources of kidney interorgan crosstalk mediators and mechanisms that upregulate them, may they be released in the kidney or in other tissues/organs, and the identification of their specific target cells and mechanisms of action in the lung. Research will need to parse apart the relationship of AKI–ALI mediators known so far in inducing or maintaining AKI–ALI, and also identify AKI–ALI mediators that contribute to the repair of remote injury.

It will be interesting to determine whether differences in remote immune responses of a given organ vary depending on the primary injury site. As an example, does the remote lung immune response in kidney–lung crosstalk differ from the one in heart–lung crosstalk? Such differences could potentially be exploited therapeutically to increase resilience to secondary organ complications after tissue injury. Future research will need to resolve whether and what roles lung metabolites and neuroimmune connections play in AKI–ALI. Finally, it will be critical to examine whether findings in animal models translate to human AKI–ALI.

References

- Zhou X, Franklin RA, Adler M, Jacox JB, Bailis W, Shyer JA, et al. Circuit design features of a stable two-cell system. *Cell*. 2018;**172**:744–57.e17.
- Rouault H, Hakim V. Different cell fates from cell-cell interactions: core architectures of two-cell bistable networks. *Biophys J*. 2012;**102**:417–26.
- Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. *Nat Rev Mol Cell Biol*. 2014;**15**:786–801.
- Bich L, Pradeu T, Moreau J-F. Understanding multicellularity: the functional organization of the intercellular space. *Front Physiol*. 2019;**10**:1170.
- Llompert-Pou JA, Talayero M, Homar J, Royo C, Grupo de trabajo de Trauma y Neurointensivismo de SEMICYUC. Multiorgan failure in the serious trauma patient. *Med Intensiva*. 2014;**38**:455–62.
- Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;**342**:1334–49.
- Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. *Nat Rev Dis Primers*. 2016;**2**:16045.
- Teixeira JP, Ambruso S, Griffin BR, Faubel S. Pulmonary consequences of acute kidney injury. *Semin Nephrol*. 2019;**39**:3–16.
- Walcher A, Faubel S, Keniston A, Dennen P. In critically ill patients requiring CRRT, AKI is associated with increased respiratory failure and death versus ESRD. *Ren Fail*. 2011;**33**:935–42.
- Faubel S, Edelstein CL. Mechanisms and mediators of lung injury after acute kidney injury. *Nat Rev Nephrol*. 2016;**12**:48–60.
- Lullo LD, Reeves PB, Bellasi A, Ronco C. Cardiorenal syndrome in acute kidney injury. *Semin Nephrol*. 2019;**39**:31–40.
- Park SW, Chen SWC, Kim M, Brown KM, Kolls JK, D'Agati VD, et al. Cytokines induce small intestine and liver injury after renal ischemia or nephrectomy. *Lab Invest*. 2011;**91**:63–84.
- Doi K. Role of kidney injury in sepsis. *J Intensive Care*. 2016;**4**:17.
- Prowle JR. Sepsis-associated AKI. *Clin J Am Soc Nephrol*. 2018;**13**:339–42.
- Bezerra R, Teles F, Mendonca PB, Damte T, Likaka A, Ferrer-Miranda E, et al. Outcomes of critically ill patients with acute kidney injury in COVID-19 infection: an observational study. *Ren Fail*. 2021;**43**:911–8.
- Darmon M, Clec'h C, Adrie C, Argaud L, Allaouchiche B, Azoulay E, et al. Acute respiratory distress syndrome and risk of AKI among critically ill patients. *Clin J Am Soc Nephrol*. 2014;**9**:1347–53.
- Lertjitbanjong P, Thongprayoon C, Cheungpasitporn W, O'Corragain OA, Srivali N, Bathini T, et al. Acute kidney injury after lung transplantation: a systematic review and meta-analysis. *J Clin Med*. 2019;**8**:1713.
- Shashaty MGS, Forker CM, Miano TA, Wu Q, Yang W, Oyster ML, et al. The association of post-lung transplant acute kidney injury with mortality is independent of primary graft dysfunction: a cohort study. *Clin Transplant*. 2019;**33**:e13678.
- Droujinine IA, Perrimon N. Defining the interorgan communication network: systemic coordination of organismal cellular processes under homeostasis and localized stress. *Front Cell Infect Microbiol*. 2013;**3**:82.
- Droujinine IA, Perrimon N. Interorgan communication pathways in physiology: focus on *Drosophila*. *Annu Rev Genet*. 2015;**50**:539–70.
- Yang D, Han Z, Oppenheim JJ. Alarmins and immunity. *Immunol Rev*. 2017;**280**:41–56.
- Dziki JL, Hussey G, Badylak SF. Alarmins of the extracellular space. *Semin Immunol*. 2018;**38**:33–9.
- Andersson U, Yang H, Harris H. High-mobility group box 1 protein (HMGB1) operates as an alarmin outside as well as inside cells. *Semin Immunol*. 2018;**38**:40–8.
- Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol*. 2010;**125**:S3–23.
- Gieseck RL, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. *Nat Rev Immunol*. 2018;**18**:62–76.
- Gameiro J, Fonseca JA, Outerelo C, Lopes JA. Acute kidney injury: from diagnosis to prevention and treatment strategies. *J Clin Med*. 2020;**9**:1704.

- 27 Faubel S, Shah PB. Immediate consequences of acute kidney injury: the impact of traditional and nontraditional complications on mortality in acute kidney injury. *Adv Chronic Kidney Dis*. 2016;**23**:179–85.
- 28 Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT. Three-year risk of cardiovascular disease among intensive care patients with acute kidney injury: a population-based cohort study. *Crit Care*. 2014;**18**:492–10.
- 29 Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol*. 2003;**14**:1549–58.
- 30 Park SW, Kim M, Kim JY, Ham A, Brown KM, Mori-Akiyama Y, et al. Paneth cell-mediated multiorgan dysfunction after acute kidney injury. *J Immunol* 2012;**189**:5421–33.
- 31 Hernando AA, Altmann C, Bhargava R, Okamura K, Bacalja J, Hunter B, et al. Prolonged acute kidney injury exacerbates lung inflammation at 7 days post-acute kidney injury. *Physiol Rep*. 2014;**2**:e12084.
- 32 Kim M, Park SW, Kim M, D'Agati VD, Lee HT. Isoflurane activates intestinal sphingosine kinase to protect against renal ischemia–reperfusion-induced liver and intestine injury. *Anesthesiology*. 2011;**114**:363–73.
- 33 Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov M, Sun Z, et al. Acute kidney injury leads to inflammation and functional changes in the brain. *J Am Soc Nephrol*. 2008;**19**:1360–70.
- 34 Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. *JAMA*. 1996;**275**:1489–94.
- 35 Mehta RL, Bouchard J, Soroko SB, Ikizler TA, Paganini EP, Chertow GM, et al. Sepsis as a cause and consequence of acute kidney injury: program to improve care in acute renal disease. *Intensive Care Med*. 2011;**37**:241–8.
- 36 Himmelfarb J, Le P, Klenzak J, Freedman S, Mcmenamin ME, Ikizler TA, et al. Impaired monocyte cytokine production in critically ill patients with acute renal failure. *Kidney Int*. 2004;**66**:2354–60.
- 37 Lee DW, Faubel S, Edelstein CL. Cytokines in acute kidney injury (AKI). *Clin Nephrol*. 2011;**76**:165–73.
- 38 Faubel S. Pulmonary complications after acute kidney injury. *Adv Chronic Kidney Dis*. 2008;**15**:284–96.
- 39 Lee SA, Cozzi M, Bush EL, Rabb H. Distant organ dysfunction in acute kidney injury: a review. *Am J Kidney Dis*. 2018;**72**:846–56.
- 40 Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. *Kidney Int*. 2016;**89**:555–64.
- 41 Doi K. The need for disruptive innovation in acute kidney injury. *Clin Exp Nephrol*. 2020;**24**:979–88.
- 42 White LE, Hassoun HT. Inflammatory mechanisms of organ crosstalk during ischemic acute kidney injury. *Int J Nephrol*. 2012;**2012**:505197.
- 43 White LE, Lie ML, Santora RJ, Rabb H, Hassoun HT. Kidney-lung crosstalk during ischemic AKI: is the T cell the missing link? *J Surg Res*. 2012;**172**:265.
- 44 Alge J, Dolan K, Angelo J, Thadani S, Virk M, Arikian AA. Two to tango: kidney-lung interaction in acute kidney injury and acute respiratory distress syndrome. *Front Pediatr*. 2021;**9**:744110.
- 45 Liu KD, Altmann C, Smits G, Krawczeski CD, Edelstein CL, Devarajan P, et al. Serum interleukin-6 and interleukin-8 are early biomarkers of acute kidney injury and predict prolonged mechanical ventilation in children undergoing cardiac surgery: a case-control study. *Crit Care*. 2009;**13**:R104.
- 46 Simmons EM, Himmelfarb J, Sezer MT, Chertow GM, Mehta RL, Paganini EP, et al. Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int*. 2004;**65**:1357–65.
- 47 Chawla LS, Seneff MG, Nelson DR, Williams M, Levy H, Kimmel PL, et al. Elevated plasma concentrations of IL-6 and elevated APACHE II score predict acute kidney injury in patients with severe sepsis. *Clin J Am Soc Nephrol*. 2007;**2**:22–30.
- 48 Zhang WR, Garg AX, Coca SG, Devereaux PJ, Eikelboom J, Kavsak P, et al. Plasma IL-6 and IL-10 concentrations predict AKI and long-term mortality in adults after cardiac surgery. *J Am Soc Nephrol*. 2015;**26**:3123–32.
- 49 Murugan R, Wen X, Shah N, Lee M, Kong L, Pike F, et al. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. *Nephrol Dial Transplant*. 2014;**29**:1854–64.
- 50 Pike F, Murugan R, Keener C, Palevsky PM, Vijayan A, Unruh M, et al. Biomarker enhanced risk prediction for adverse outcomes in critically ill patients receiving RRT. *Clin J Am Soc Nephrol*. 2015;**10**:1332–9.
- 51 Liangos O, Kolyada A, Tighiouart H, Perianayagam MC, Wald R, Jaber BL. Interleukin-8 and acute kidney injury following cardiopulmonary bypass: a prospective cohort study. *Nephron Clin Pract*. 2009;**113**:c148–54.
- 52 Bhargava R, Altmann CJ, Hernando AA, Webb RG, Okamura K, Yang Y, et al. Acute lung injury and acute kidney injury are established by four hours in experimental sepsis and are improved with pre, but not post, sepsis administration of TNF- α antibodies. *PLoS One*. 2013;**8**:e79037.
- 53 Liu KD, Matthay MA. Advances in critical care for the nephrologist: acute lung injury/ARDS. *Clin J Am Soc Nephrol*. 2008;**3**:578–86.

- 54 Puneet P, Mochhala S, Bhatia M. Chemokines in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2005;**288**:L3–15.
- 55 Kim DJ, Park SH, Sheen MR, Jeon US, Kim SW, Koh ES, et al. Comparison of experimental lung injury from acute renal failure with injury due to sepsis. *Respiration*. 2006;**73**:815–24.
- 56 Colletti LM, Kunkel SL, Walz A, Burdick MD, Kunkel RG, Wilke CA, et al. Chemokine expression during hepatic ischemia/reperfusion-induced lung injury in the rat. The role of epithelial neutrophil activating protein. *J Clin Invest*. 1995;**95**:134–41.
- 57 Colletti LM, Cortis A, Lukacs N, Kunkel SL, Green M, Strieter RM. Tumor necrosis factor up-regulates intercellular adhesion molecule 1, which is important in the neutrophil-dependent lung and liver injury associated with hepatic ischemia and reperfusion in the rat. *Shock*. 1998;**10**:182–91.
- 58 Hirano Y, Aziz M, Yang W-L, Ochani M, Wang P. Neutralization of osteopontin ameliorates acute lung injury induced by intestinal ischemia-reperfusion. *Shock*. 2016;**46**:431–8.
- 59 Hirano Y, Aziz M, Yang W-L, Wang Z, Zhou M, Ochani M, et al. Neutralization of osteopontin attenuates neutrophil migration in sepsis-induced acute lung injury. *Crit Care*. 2015;**19**:53.
- 60 Seekamp A, Mulligan MS, Till GO, Smith CW, Miyasaka M, Tamatani T, et al. Role of beta 2 integrins and ICAM-1 in lung injury following ischemia-reperfusion of rat hind limbs. *Am J Pathol*. 1993;**143**:464–72.
- 61 Welbourn R, Goldman G, O'Riordain M, Lindsay TF, Paterson IS, Kobzik L, et al. Role for tumor necrosis factor as mediator of lung injury following lower torso ischemia. *J Appl Physiol*. 1991;**70**:2645–9.
- 62 Yoshidome H, Lentsch AB, Cheadle WG, Miller FN, Edwards MJ. Enhanced pulmonary expression of CXC chemokines during hepatic ischemia/reperfusion-induced lung injury in mice. *J Surg Res*. 1999;**81**:33–7.
- 63 Hoke TS, Douglas IS, Klein CL, He Z, Fang W, Thurman JM, et al. Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *J Am Soc Nephrol*. 2007;**18**:155–64.
- 64 Klein CL, Hoke TS, Fang W-F, Altmann CJ, Douglas IS, Faubel S. Interleukin-6 mediates lung injury following ischemic acute kidney injury or bilateral nephrectomy. *Kidney Int*. 2008;**74**:901–9.
- 65 Ahuja N, Hernandez AA, Altmann C, Bhargava R, Bacalja J, Webb RG, et al. Circulating IL-6 mediates lung injury via CXCL1 production after acute kidney injury in mice. *Am J Physiol Renal Physiol*. 2012;**303**:F864–72.
- 66 Ishii T, Doi K, Okamoto K, Imamura M, Dohi M, Yamamoto K, et al. Neutrophil elastase contributes to acute lung injury induced by bilateral nephrectomy. *Am J Pathol*. 2010;**177**:1665–73.
- 67 Hassoun HT, Grigoryev DN, Lie ML, Liu M, Cheadle C, Tudor RM, et al. Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. *Am J Physiol Renal Physiol*. 2007;**293**:F30–40.
- 68 Khamissi FZ, Ning L, Kefaloyianni E, Dun H, Arthanarisami A, Keller A, et al. Identification of kidney injury released circulating osteopontin as causal agent of respiratory failure. *Sci Adv*. 2022;**8**:1–19. <https://doi.org/10.1126/sciadv.abm5900>
- 69 Andres-Hernando A, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transpl*. 2012;**27**:4339–47.
- 70 Hernandez AA, Okamura K, Bhargava R, Kiekhäfer CM, Soranno D, Kirkbride-Romeo LA, et al. Circulating IL-6 upregulates IL-10 production in splenic CD4+ T cells and limits acute kidney injury-induced lung inflammation. *Kidney Int*. 2017;**91**:1057–69.
- 71 Lowenstein J, Nigam SK. Uremic toxins in organ crosstalk. *Front Med*. 2021;**8**:592602.
- 72 Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. *Toxins*. 2021;**13**:142.
- 73 Wu W, Bush KT, Nigam SK. Key role for the organic anion transporters, OAT1 and OAT3, in the in vivo handling of uremic toxins and solutes. *Sci Rep*. 2017;**7**:4939.
- 74 Adelibieke Y, Yisireyli M, Ng H-Y, Saito S, Nishijima F, Niwa T. Indoxyl sulfate induces IL-6 expression in vascular endothelial and smooth muscle cells through OAT3-mediated uptake and activation of AhR/NF-κB pathway. *Nephron Exp Nephrol*. 2014;**128**:1–8.
- 75 Kawakami T, Inagi R, Wada T, Tanaka T, Fujita T, Nangaku M. Indoxyl sulfate inhibits proliferation of human proximal tubular cells via endoplasmic reticulum stress. *Am J Physiol Renal Physiol*. 2010;**299**:F568–76.
- 76 Lekawanvijit S, Adrahtas A, Kelly DJ, Kompa AR, Wang BH, Krum H. Does indoxyl sulfate, a uraemic toxin, have direct effects on cardiac fibroblasts and myocytes? *Eur Heart J*. 2010;**31**:1771–9.
- 77 Rabb H, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int*. 2003;**63**:600–6.
- 78 Yabuuchi N, Sagata M, Saigo C, Yoneda G, Yamamoto Y, Nomura Y, et al. Indoxyl sulfate as a mediator involved in dysregulation of pulmonary aquaporin-5 in acute lung injury caused by acute kidney injury. *Int J Mol Sci*. 2016;**18**:11.

- 79 Chang J-F, Liang S-S, Thanasekaran P, Chang H-W, Wen L-L, Chen C-H, et al. Translational medicine in pulmonary-renal crosstalk: therapeutic targeting of p-cresyl sulfate triggered nonspecific ROS and chemoattractants in dyspneic patients with uremic lung injury. *J Clin Med*. 2018;**7**:266.
- 80 Ma T, Liu Z. Functions of aquaporin 1 and α -epithelial Na⁺ channel in rat acute lung injury induced by acute ischemic kidney injury. *Int Urol Nephrol*. 2013;**45**:1187–96.
- 81 Meduri GU, Kohler G, Headley S, Tolley E, Stentz F, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS persistent elevation over time predicts poor outcome. *Chest*. 1995;**108**:1303–14.
- 82 Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS plasma IL-1 β and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest*. 1995;**107**:1062–73.
- 83 Belperio JA, Keane MP, Burdick MD, Londhe V, Xue YY, Li K, et al. Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. *J Clin Invest*. 2002;**110**:1703–16.
- 84 Faubel S, Lewis EC, Reznikov L, Ljubanovic D, Hoke TS, Somers H, et al. Cisplatin-induced acute renal failure is associated with an increase in the cytokines interleukin (IL)-1 β , IL-18, IL-6, and neutrophil infiltration in the kidney. *J Pharmacol Exp Ther*. 2007;**322**:8–15.
- 85 Kielar ML, John R, Bennett M, Richardson JA, Shelton JM, Chen L, et al. Maladaptive role of IL-6 in ischemic acute renal failure. *J Am Soc Nephrol*. 2005;**16**:3315–25.
- 86 Hernando AA, Altmann C, Ahuja N, Lanasa MA, Nemenoff R, He Z, et al. Splenectomy exacerbates lung injury after ischemic acute kidney injury in mice. *Am J Physiol Renal Physiol*. 2011;**301**:F907–16.
- 87 Bhargava R, Janssen W, Altmann C, Hernando AA, Okamura K, Vandivier RW, et al. Intratracheal IL-6 protects against lung inflammation in direct, but not indirect, causes of acute lung injury in mice. *PLoS One*. 2013;**8**:e61405.
- 88 Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest*. 2007;**117**:289–96.
- 89 Hassoun HT, Lie ML, Grigoryev DN, Liu M, Tuder RM, Rabb H. Kidney ischemia-reperfusion injury induces caspase-dependent pulmonary apoptosis. *Am J Physiol Renal Physiol*. 2009;**297**:F125–37.
- 90 White LE, Cui Y, Shelak CMF, Lie ML, Hassoun HT. Lung endothelial cell apoptosis during ischemic acute kidney injury. *Shock*. 2012;**38**:320–7.
- 91 White LE, Santora RJ, Cui Y, Moore FA, Hassoun HT. TNFR1-dependent pulmonary apoptosis during ischemic acute kidney injury. *Am J Physiol Lung Cell Mol Physiol*. 2012;**303**:L449–59.
- 92 Kirita Y, Wu H, Uchimura K, Wilson PC, Humphreys BD. Cell profiling of mouse acute kidney injury reveals conserved cellular responses to injury. *Proc National Acad Sci USA*. 2020;**117**:15874–83.
- 93 Doi K, Ishizu T, Tsukamoto-Sumida M, Hiruma T, Yamashita T, Ogasawara E, et al. The high-mobility group protein B1-Toll-like receptor 4 pathway contributes to the acute lung injury induced by bilateral nephrectomy. *Kidney Int*. 2014;**86**:316–26.
- 94 Wu H, Ma J, Wang P, Corpuz TM, Panchapakesan U, Wyburn KR, et al. HMGB1 contributes to kidney ischemia reperfusion injury. *J Am Soc Nephrol*. 2010;**21**:1878–90.
- 95 Zakiyanov O, Kriha V, Vachek J, Zima T, Tesar V, Kalousova M. Placental growth factor, pregnancy-associated plasma protein-A, soluble receptor for advanced glycation end products, extracellular newly identified receptor for receptor for advanced glycation end products binding protein and high mobility group box 1 levels in patients with acute kidney injury: a cross sectional study. *BMC Nephrol*. 2013;**14**:245.
- 96 Kruger TE, Miller AH, Godwin AK, Wang J. Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers. *Crit Rev Oncol Hemat*. 2014;**89**:330–41.
- 97 Ramaiah SK, Rittling S. Pathophysiological role of osteopontin in hepatic inflammation, toxicity, and cancer. *Toxicol Sci*. 2008;**103**:4–13.
- 98 Fisher LW, Torchia DA, Fohr B, Young MF, Fedarko NS. Flexible structures of SIBLING proteins, bone sialoprotein, and osteopontin. *Biochem Biophys Res Commun*. 2001;**280**:460–5.
- 99 Pichler R, Giachelli CM, Lombardi D, Pippin J, Gordon K, Alpers CE, et al. Tubulointerstitial disease in glomerulonephritis. Potential role of osteopontin (uropontin). *Am J Pathol*. 1994;**144**:915–26.
- 100 Oldberg A, Franzén A, Heinegård D. Cloning and sequence analysis of rat bone sialoprotein (osteopontin) cDNA reveals an Arg-Gly-Asp cell-binding sequence. *Proc National Acad Sci USA*. 1986;**83**:8819–23.
- 101 Denhardt DT, Guo X. Osteopontin: a protein with diverse functions. *FASEB J*. 1993;**7**:1475–82.
- 102 Murugaian G, Mittal A, Weiner HL. Increased osteopontin expression in dendritic cells amplifies IL-17 production by CD4⁺ T cells in experimental autoimmune encephalomyelitis and in multiple sclerosis. *J Immunol*. 2008;**181**:7480–8.
- 103 Ashkar S, Weber GF, Panoutsakopoulou V, Sanchirico ME, Jansson M, Zawaideh S, et al. Eta-1 (osteopontin): an early component of type-1 (cell-mediated) immunity. *Science*. 2000;**287**:860–4.

- 104 Castello LM, Baldrighi M, Molinari L, Salmi L, Cantaluppi V, Vaschetto R, et al. The role of osteopontin as a diagnostic and prognostic biomarker in sepsis and septic shock. *Cells*. 2019;**8**:174.
- 105 Carbone F, Bonaventura A, Vecchiè A, Meessen J, Minetti S, Elia E, et al. Early osteopontin levels predict mortality in patients with septic shock. *Eur J Intern Med*. 2020;**78**:113–20.
- 106 Zhao H, Chen Q, Huang H, Suen KC, Alam A, Cui J, et al. Osteopontin mediates necroptosis in lung injury after transplantation of ischaemic renal allografts in rats. *Br J Anaesth*. 2019;**123**:519–30.
- 107 Muteliefu G, Enomoto A, Jiang P, Takahashi M, Niwa T. Indoxyl sulphate induces oxidative stress and the expression of osteoblast-specific proteins in vascular smooth muscle cells. *Nephrol Dial Transplant*. 2009;**24**:2051–8.
- 108 Adijiang A, Goto S, Uramoto S, Nishijima F, Niwa T. Indoxyl sulphate promotes aortic calcification with expression of osteoblast-specific proteins in hypertensive rats. *Nephrol Dial Transplant*. 2008;**23**:1892–901.
- 109 Roderburg C, Benz F, Cardenas DV, Lutz M, Hippe H-J, Luedde T, et al. Persistently elevated osteopontin serum levels predict mortality in critically ill patients. *Crit Care*. 2015;**19**:271.
- 110 Lorenzen JM, Hafer C, Faulhaber-Walter R, Kumpers P, Kielstein JT, Haller H, et al. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2010;**26**:531–7.
- 111 Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, et al. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med*. 2007;**35**:2755–61.
- 112 Takahashi F, Takahashi K, Shimizu K, Cui R, Tada N, Takahashi H, et al. Osteopontin is strongly expressed by alveolar macrophages in the lungs of acute respiratory distress syndrome. *Lung*. 2004;**182**:173–85.
- 113 Kasetty G, Papareddy P, Bhongir RKV, Ali MN, Mori M, Wygrecka M, et al. Osteopontin protects against lung injury caused by extracellular histones. *Mucosal Immunol*. 2019;**12**:39–50.
- 114 Jovic S, Shikhagaie M, Mörgelin M, Erjefält JS, Kjellström S, Egesten A. Osteopontin is increased in cystic fibrosis and can skew the functional balance between ELR-positive and ELR-negative CXC-chemokines. *J Cyst Fibros*. 2015;**14**:453–63.
- 115 Papaporfyriou A, Loukides S, Kostikas K, Simoes DCM, Papatheodorou G, Konstantellou E, et al. Increased levels of osteopontin in sputum supernatant in patients with COPD. *Chest*. 2014;**146**:951–8.
- 116 Samitas K, Zervas E, Vittorakis S, Semitekolou M, Alissafi T, Bossios A, et al. Osteopontin expression and relation to disease severity in human asthma. *Eur Respir J*. 2010;**37**:331–41.
- 117 Christov M, Neyra JA, Gupta S, Leaf DE. Fibroblast growth factor 23 and klotho in AKI. *Semin Nephrol*. 2019;**39**:57–75.
- 118 Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature*. 1997;**390**:45–51.
- 119 Sugiura H, Yoshida T, Shiohira S, Kohei J, Mitobe M, Kurosu H, et al. Reduced Klotho expression level in kidney aggravates renal interstitial fibrosis. *Am J Physiol Renal Physiol*. 2012;**302**:F1252–64.
- 120 Doi S, Zou Y, Togao O, Pastor JV, John GB, Wang L, et al. Klotho inhibits transforming growth factor- β 1 (TGF- β 1) signaling and suppresses renal fibrosis and cancer metastasis in mice. *J Biol Chem*. 2011;**286**:8655–65.
- 121 Hu MC, Bian A, Neyra J, Zhan M. Klotho, stem cells, and aging. *Clin Interv Aging*. 2015;**10**:1233–43.
- 122 Shi M, Flores B, Gillings N, Bian A, Cho HJ, Yan S, et al. α Klotho mitigates progression of AKI to CKD through activation of autophagy. *J Am Soc Nephrol*. 2016;**27**:2331–45.
- 123 Kim AJ, Ro H, Kim H, Chang JH, Lee HH, Chung W, et al. Klotho and S100A8/A9 as discriminative markers between pre-renal and intrinsic acute kidney injury. *PLoS One*. 2016;**11**:e0147255.
- 124 Ravikumar P, Li L, Ye J, Shi M, Taniguchi M, Zhang J, et al. α Klotho deficiency in acute kidney injury contributes to lung damage. *J Appl Physiol*. 2016;**120**:723–32.
- 125 Liu S, Vierthaler L, Tang W, Zhou J, Quarles LD. FGFR3 and FGFR4 do not mediate renal effects of FGF23. *J Am Soc Nephrol*. 2008;**19**:2342–50.
- 126 Yazaki N, Fujita H, Ohta M, Kawasaki T, Itoh N. The structure and expression of the FGF receptor-1 mRNA isoforms in rat tissues. *Biochim Biophys Acta*. 1993;**1172**:37–42.
- 127 Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;**444**:770–4.
- 128 Awad AS, Rouse M, Huang L, Vergis AL, Reutershan J, Cathro HP, et al. Compartmentalization of neutrophils in the kidney and lung following acute ischemic kidney injury. *Kidney Int*. 2009;**75**:689–98.
- 129 Hopps HC, Wissler RW. Uremic pneumonitis. *Am J Pathol*. 1955;**31**:261–73.
- 130 Kramer AA, Postler G, Salhab KF, Mendez C, Carey LC, Rabb H. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int*. 1999;**55**:2362–7.
- 131 Altmann C, Hernando AA, McMahan RH, Ahuja N, He Z, Rivard CJ, et al. Macrophages mediate lung

- inflammation in a mouse model of ischemic acute kidney injury. *Am J Physiol Renal Physiol.* 2012;**302**:F421–32.
- 132 Karimi Z, Ketabchi F, Alebrahimdehkordi N, Fatemikia H, Owji SM, Moosavi SMS. Renal ischemia/reperfusion against nephrectomy for induction of acute lung injury in rats. *Ren Fail.* 2016;**38**:1503–15.
 - 133 Lie ML, White LE, Santora RJ, Park JM, Rabb H, Hassoun HT. Lung T lymphocyte trafficking and activation during ischemic acute kidney injury. *J Immunol.* 2012;**189**, 2843–51.
 - 134 Mulay SR, Anders H-J. Neutrophils and neutrophil extracellular traps regulate immune responses in health and disease. *Cells.* 2020;**9**:2130.
 - 135 Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol.* 2018;**18**:134–47.
 - 136 Li P, Li M, Lindberg MR, Kennett MJ, Xiong N, Wang Y. PAD4 is essential for antibacterial innate immunity mediated by neutrophil extracellular traps. *J Exp Med.* 2010;**207**:1853–62.
 - 137 Nakazawa D, Kumar SV, Marschner J, Desai J, Holderied A, Rath L, et al. Histones and neutrophil extracellular traps enhance tubular necrosis and remote organ injury in ischemic AKI. *J Am Soc Nephrol.* 2017;**28**:1753–68.
 - 138 Fox BM, Gil H-W, Kirkbride-Romeo L, Bagchi RA, Wennersten SA, Haefner KR, et al. Metabolomics assessment reveals oxidative stress and altered energy production in the heart after ischemic acute kidney injury in mice. *Kidney Int.* 2019;**95**:590–610.
 - 139 Hepokoski M, Wang J, Li K, Li Y, Gupta P, Mai T, et al. Altered lung metabolism and mitochondrial DAMPs in lung injury due to acute kidney injury. *Am J Physiol Lung Cell Mol Physiol.* 2021;**320**:L821–31.
 - 140 Ambruso SL, Gil H-W, Fox B, Park B, Altmann C, Bagchi RA, et al. Lung metabolomics after ischemic acute kidney injury reveals increased oxidative stress, altered energy production, and ATP depletion. *Am J Physiol Lung Cell Mol Physiol.* 2021;**321**:L50–64.
 - 141 Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010;**464**:104–7.
 - 142 Chaung WW, Wu R, Ji Y, Dong W, Wang P. Mitochondrial transcription factor A is a proinflammatory mediator in hemorrhagic shock. *Int J Mol Med.* 2012;**30**:199–203.
 - 143 Ordoas-Montanes J, Rakoff-Nahoum S, Huang S, Riol-Blanco L, Barreiro O, von Andrian UH. The regulation of immunological processes by peripheral neurons in homeostasis and disease. *Trends Immunol.* 2015;**36**:578–604.
 - 144 Pavlov VA, Tracey KJ. Neural regulation of immunity: molecular mechanisms and clinical translation. *Nat Neurosci.* 2017;**20**:156–66.
 - 145 Okusa MD, Rosin DL, Tracey KJ. Targeting neural reflex circuits in immunity to treat kidney disease. *Nat Rev Nephrol.* 2017;**13**:669–80.
 - 146 Bellinger DL, Felten SY, Lorton D, Felten DL. Origin of noradrenergic innervation of the spleen in rats. *Brain Behav Immun.* 1989;**3**:291–311.
 - 147 Felten DL, Ackerman KD, Wiegand SJ, Felten SY. Noradrenergic sympathetic innervation of the spleen: I. Nerve fibers associate with lymphocytes and macrophages in specific compartments of the splenic white pulp. *J Neurosci Res.* 1987;**18**:28–36.
 - 148 Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. *J Immunol.* 1985;**135**:755s–65s.
 - 149 Williams JM, Peterson RG, Shea PA, Schmedtje JF, Bauer DC, Felten DL. Sympathetic innervation of murine thymus and spleen: evidence for a functional link between the nervous and immune systems. *Brain Res Bull.* 1981;**6**:83–94.
 - 150 Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and therapeutic relevance of neuro-immune communication. *Immunity.* 2017;**46**:927–42.
 - 151 Chiu IM, Heesters BA, Ghasemlou N, Hehn CAV, Zhao F, Tran J, et al. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature.* 2013;**501**:52–7.
 - 152 Pinho-Ribeiro FA, Verri WA, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends Immunol.* 2017;**38**:5–19.
 - 153 Meroni E, Stakenborg N, Gomez-Pinilla PJ, Hertogh GD, Goverse G, Matteoli G, et al. Functional characterization of oxazolone-induced colitis and survival improvement by vagus nerve stimulation. *PLoS One.* 2018;**13**:e0197487.
 - 154 Rosas-Ballina M, Ochani M, Parrish WR, Ochani K, Harris YT, Huston JM, et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. *Proc National Acad Sci USA.* 2008;**105**:11008–13.
 - 155 Inoue T, Abe C, Sung SJ, Moscalu S, Jankowski J, Huang L, et al. Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through $\alpha 7$ nAChR⁺ splenocytes. *J Clin Invest.* 2016;**126**:1939–52.
 - 156 Tanaka S, Abe C, Abbott SGB, Zheng S, Yamaoka Y, Lipsey JE, et al. Vagus nerve stimulation activates two distinct neuroimmune circuits converging in the spleen to protect mice from kidney injury. *Proc National Acad Sci USA.* 2021;**118**:e2021758118.