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CKJ REVIEW

New approaches to acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is a common and serious clinical syndrome that involves complex interplay between different cellular, molecular, metabolic and immunologic mechanisms. Elucidating these pathophysiologic mechanisms is crucial to identify novel biomarkers and therapies. Recent innovative methodologies and the advancement of existing technologies has accelerated our understanding of AKI and led to unexpected new therapeutic candidates. The aim of this review is to introduce and update the reader about recent developments applying novel technologies in omics, imaging, nanomedicine and artificial intelligence to AKI research, plus to provide examples where this can be translated to improve patient care.

Keywords: AKI, artificial intelligence, imaging, nanomedicine, omics

INTRODUCTION

Acute kidney injury (AKI) affects approximately 2%–5% of hospitalized patients and is very common after solid organ transplant. Furthermore, AKI occurs in up to 50% patients in the intensive care unit and significantly increases their risk of death [1, 2]. A complex interplay between several different pathophysiologic mechanisms, including metabolic, immunologic, genetic and others, determines either full recovery from AKI or progression to chronic kidney disease (CKD) [3–6]. Understanding these pathophysiologic mechanisms and their interactions is crucial for understanding AKI, and discovering novel diagnostics and therapies. Recent development of advanced methodologies and refinement of existing technologies has had a major impact on AKI research, which in turn is leading to exciting novel translational applications to patients. This review is focused on application of novel technologies including omics, nano medicine, imaging and artificial intelligence for AKI research, and early translation opportunities for patients. These methods are fast-evolving making it difficult for us to include all relevant studies in this review. The reader is advised to consult more detailed reviews and original articles related to each of the major approaches covered in this paper. In the course of this review, it is important to distinguish between experimental models and the clinical picture. In experimental models, the type of injury is known and intervention is mostly pre-injury. In contrast, the cause of injury in humans may not always be known and diagnostics/interventions usually start after the initial injury has occurred.

OMICS TECHNOLOGIES IN AKI

The term “omics” refers to high throughput, unbiased measurements of the molecular/chemical repertoire of a biological compartment in its entirety and the analysis using advanced computational approaches to find patterns and relationships within the data [7]. In the past decade, “omics” technologies have become increasingly affordable and accessible to large number of researchers. The most important “omics” used in kidney diseases include transcriptomics, proteomics, metabolomics and metagenomics [7–12] allowing the quantification and characterization of multiple different types of biochemical materials [13]. Altogether, “omics” have elucidated cellular and molecular processes involved in AKI and led to the identification of novel biomarkers and candidate therapeutics [14–18]. With the ongoing advancements and integration of different “omics” technologies, it is likely that “omics” will transform our understanding of

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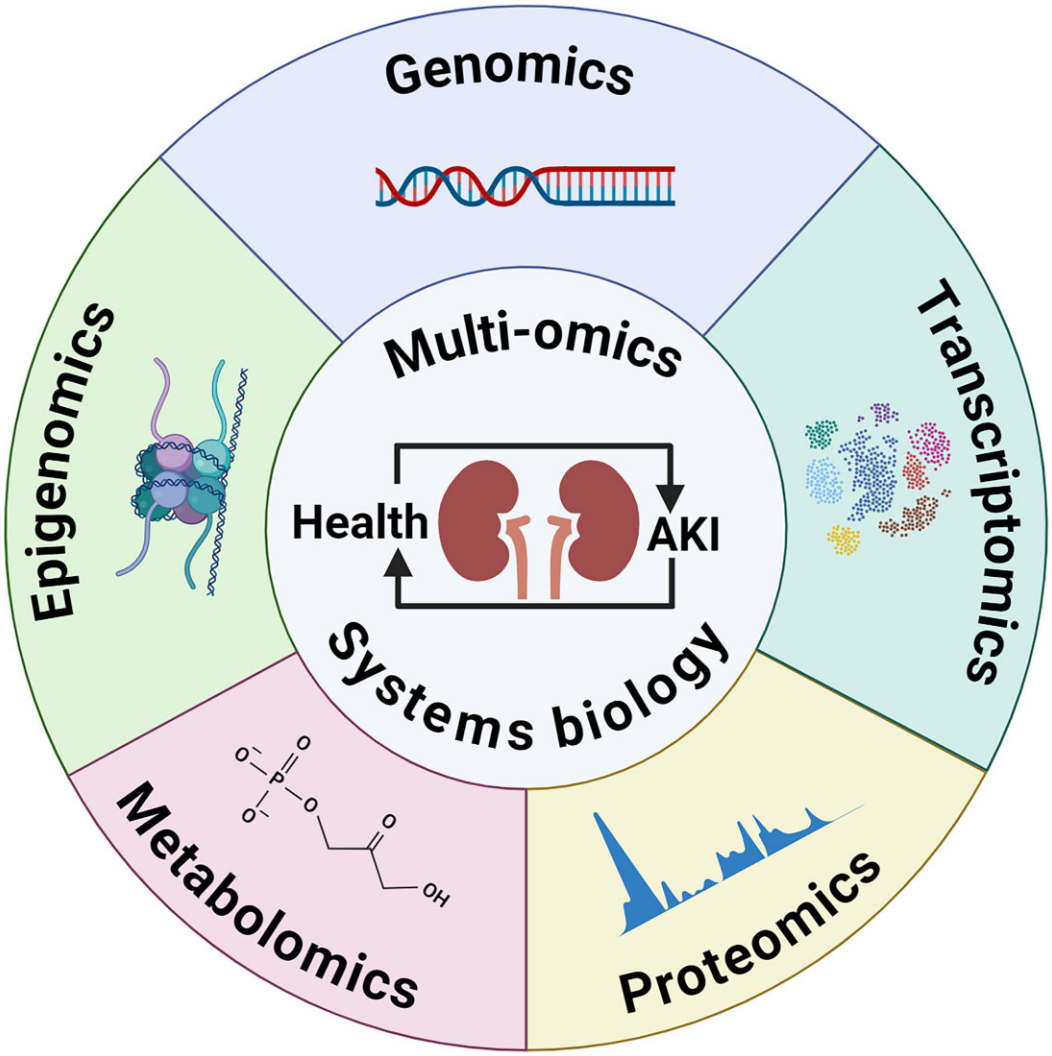

Figure 1: A multi-omics approach to AKI. Single omics data can be integrated into multiple omics and combined with systems biology. These approaches can be used to discover the pathophysiological mechanisms of AKI, novel biomarkers and therapeutic targets. Figure adapted from Qiao and Cui, *Front Immunol* 2022 [9].

the pathogenesis of AKI, diagnosis and treatment (Fig. 1) [7, 9, 10, 13]. Select recent examples of the use of "omics" technology in AKI research are reviewed here.

Transcriptomics

Mammalian kidneys eliminate waste from the blood, preserve fluid balance, secrete hormones and regulate blood pressure [19]. This is accomplished by a host of different type of cells in the nephron, made up of more than 20 different cell types [19, 20]. Additionally, perivascular cells, immune cells, endothelial cells, podocytes, interstitial fibroblasts and other cells are present in the kidney and play essential roles in maintaining kidney structure and function. Investigating transcriptional changes in these cellular compartments during homeostasis and following AKI is important for understanding cellular response to different stresses, interactions between different cell types and discovery of novel therapeutic targets. Until recently, cell type–specific interrogation was nearly impossible. However, recent developments in microfluidics and sequencing technologies have led to the development of single-cell RNA sequencing (scRNA-Seq), allowing untargeted sequencing of total RNA content at the single-cell level in multiple kidney diseases [21–27]. One of the earliest uses of scRNA-Seq in AKI revealed heterogeneity in the regulatory T (Treg) cell population in the acute and chronic phases after AKI [28], confirming previous work with more traditional technologies demonstrating the role for Tregs in mediating protection from AKI and AKI-induced fibrosis [29]. Subsequent scRNA-Seq studies (Table 1) have clarified the response of different cell types in AKI [30], elucidated AKI-associated dedifferentiation programs and potential pathologic ligand–receptor crosstalk [31], and identified unique inflammatory macrophage subsets [32], transcriptional changes during AKI-to-CKD [33, 34] and development of cancer [35]. In a recent study, scRNA-Seq was used to investigate the role of novel immune checkpoint molecule T-cell immunoreceptor with Ig and ITIM domains (TIGIT) in AKI [36]. Another recent study using scRNA-Seq revealed *SRY-box containing gene 9* (*Sox9*) as an important on–off sensor of epithelial repair, the activity of which determines regeneration or development of fibrosis after AKI [37]. A slightly modified version of scRNA-Seq is single nucleus (sn)RNA-Seq where RNA content present in the nucleus is studied instead of

Table 1: Recent scRNA-Seq and spatial transcriptomics studies in AKI.

Disease model	Species	Summary	Reference
IR-AKI	C57BL/6N and Foxp3-EGFP, male and female mice	scRNA-Seq used to study immune cell gene expression in AKI mouse model showed heterogeneity in kidney Treg cell population	Duraes *et al*. 2020 [28]
UIRI-AKI	Swiss-Webster (CFW) mice	AKI-associated dedifferentiation transcriptomic changes, ligand-receptor crosstalk and novel genes in AKI	Rudman-Melnick *et al*. 2020 [31]
UIRI/BIRI-AKI	C57BL/6 J mice	scRNA-seq analysis identified a distinct S100a9^{hi}Ly6c^{hi} macrophage population that initiates and amplifies the inflammatory response during the acute stage of kidney injury	Yao *et al*. 2022 [32]
IR-AKI	Pax2/NICD1 and Pax2/NICD1/Confetti mice	Validated scRNA-Seq data from human samples in mice to demonstrate that AKI induces papillary tumors by promoting clonal expansion of renal progenitors	Peired *et al*. 2020 [35]
IR and cisplatin AKI	C57BL/6J mice	Novel immune checkpoint TIGIT expression increases in mouse and human kidney T cells during AKI, worsens AKI outcomes, and is a potential therapeutic target for AKI	Noel *et al*. 2023 [36]
IRI-AKI	WT and Sox9 KO mice	Sox9 is an important on-off switch that control either full recovery or development of fibrosis after AKI	Aggarwal *et al*. 2024 [37]
COVID-19-AKI	Human	snRNA-Seq of kidney biopsies and urine cell RNA sequencing and found cell specific markers of COVID-19 AKI	Ghag *et al*. 2023 [38]
IR-AKI	Mice	Global and cell type-specific transcriptional changes in the nephron preceded the extensive cell cycle response induced by AKI. Adaptive repair is associated with decreased expression of genes encoding transmembrane transport proteins, which are essential for kidney function	Gerhardt *et al*. 2023 [39]
IRI-AKI	C57BL/6J mice	Region-specific and injury-induced loss of differentiation markers as well as region-specific injury and repair transcriptional responses.	Dixon *et al*. 2022 [42]
IRI-AKI	C57BL/6J mice	scRNA-Seq and spatial transcriptomics analysis shows kidney double negative T cell have distinct transcription profile in normal and ischemic mouse kidneys	Gharaie *et al*. 2023 [15]
Healthy, AKI, CKD	Human	Multi-omic approach found transcriptomic profiles, regulatory factors and spatial localizations spanning the entire kidney	Lake *et al*. 2023 [26]

IRI, ischemia reperfusion injury; UIRI, unilaterla ischemia reperfusion injury; BIRI, bilateral ischemia reperfusion injury.

the whole cell. snRNA-Seq is suitable for frozen/fixed samples and cell types where isolation of intact cell is technically difficult. The use of snRNA-Seq in kidney biopsies and urine cells has been used to identify marker genes in COVID-19 patients with AKI [38]. Additionally, novel adaptive and maladaptive repair markers in post-AKI kidneys were found using the snRNA-Seq approach [34, 39].

Although, scRNA-Seq and snRNA-Seq enable global transcriptional profiling, the inherent nature of these technologies results in the loss of spatial information about where in the kidney these transcriptional changes occur. Spatial transcriptomics (ST) is a novel approach that allows transcriptional profiling and mapping to the exact location in the organ. Recently, ST was used to define injury-specific microenvironments in the adult mouse kidney and identified novel cellular interactions in regeneration and disease [40]. Other studies have used ST to spatially resolve transcriptional changes in female mouse kidney after AKI [41, 42] and localize the distinct microenvironment occupied by resident macrophages in the kidney [43]. Additionally, ST-based kidney transcriptomic profiling revealed that injured proximal tubule cells exhibit increased macrophage and lymphocyte contacts during AKI-to-CKD transition [34]. Integration of scRNA-Seq and ST approaches has further improved the study of transcriptional changes in kidney tissue during AKI. For example, integrated spatial and single cell transcriptomics was used to localize epithelial cell-immune cross-talk following ischemia reperfusion (IR)- and cecal ligation and puncture (CLP)-induced AKI. The investigators identified patterns of co-localization between immune and epithelial cells with activation of transcription factor 3 (Atf3) and midkine (Mdk) as important chemotactic factors in S3 proximal tubules [44]. Similarly, an integrated approach using innovative data deconvolution algorithms was used to identify molecular signature and spatial dynamics of double-negative (DN) T cells in normal

kidneys and during AKI [15]. Results from this study revealed the *Fcer1g* gene as a putative DN T-cell marker in both the normal and ischemic kidney. It was also found that expression of *Kcnq5*, which encodes the Kv7.5 potassium channel, was significantly higher in normal kidney DN T cells compared with normal $CD4^+$, $CD8^+$ and ischemic kidney DN T cells (Fig. 2). The integrated use of these technologies has also been used to develop an atlas of healthy and injured human kidney by the Kidney Precision Medicine Project (KPMP) investigators [26]. KPMP and other research groups have developed interactive data visualization tools that allow exploration and visualization of gene of interest (atlas.kpmp.org; humphreyslab.com/SingleCell).

Metabolomics

Metabolism is a combination of essential cellular functions, including synthesis of complex macro molecules from simpler molecules (anabolism), breakdown of molecules to generate energy (catabolism) and degradation of toxins, drugs and cellular debris (waste disposal) to maintain homeostasis [45]. Metabolomics is the measurement of the metabolites that are generated as a result of cellular metabolism [46, 47]. Kidneys play vital roles in maintaining homeostasis through precise osmoregulation, maintenance of ionic balance and excretion of waste metabolites. Under homeostatic conditions, different parts of the kidney have different metabolic demands. In general, the renal medulla relies predominantly on glycolysis, whereas the cortex depends on oxidative phosphorylation (OXPHOS) for meeting energy demands [48]. AKI results in metabolic reprograming in response to altered energy demand and supply [49]. Several recent studies (Table 2) using gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS) platforms plus nuclear magnetic resonance (NMR)-based metabolite measurements show that AKI due to IR, cisplatin or sepsis resulted in significant mitochondrial damage plus oxygen and nutrient deprivation that subsequently led to reduced glycolysis and mitochondrial bioenergetics [50–54]. These studies also found disruptions in the pentose phosphate pathway, amino acid metabolism and ketone bodies following AKI. A novel approach was the use of high dimensional flow cytometric panel evaluation of key metabolism related proteins to assess kidney T-cell specific metabolic changes during AKI. This approach showed significant reduction in voltage-dependent anion channel 1 (marker of OXPHOS activity) and mTOR expression, with increased expression of histone H3 lysine 27 (marker of histone methylation) and glutaminase in post-AKI kidneys. Furthermore, *in vivo* administration of glutamine antagonist, JHU083, attenuated kidney injury and reduced T-cell activation and proliferation in ischemic and nephrotoxic AKI [55]. In addition to the injury process, metabolic reprogramming characterized by a metabolic shift toward glycolysis, decreased fatty acid β-oxidation and amino acid metabolism, occurred during the repair phase [50]. A recent study found that trimethylamine N-oxide (TMAO) is a key metabolite associated with AKI-to-CKD transition, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2) activation was identified as a key regulator of TMAO-related AKI-to-CKD transition both *in vivo* and *in vitro* [16]. These findings highlight potential therapeutic targeting of metabolic reprogramming of kidney cells to restore metabolic homeostasis and mitigate kidney injury. Furthermore, these metabolic changes can be used as potential biomarkers to assist diagnosis of AKI in context of other diseases [56–59].

Epigenomics

Epigenomics is the study of the epigenetic modifications including DNA methylation, histone acetylation, phosphorylation, ubiquitination, micro-RNA, ADP-ribosylation, deamination, proline isomerization and RNA methylation. Epigenetic modifications are important regulators of gene expression and inadequate or dysregulated epigenetic modifications have been linked to various diseases including AKI and progression of AKI-to-CKD (Fig. 3) [60–62]. Hypoxic conditions during and after AKI result in long-term epigenetic modifications known as "hypoxia memory". The role of histone 3, lysine 4 and lysine 27 trimethylation is well established, and promoted CKD development following experimental unilateral ureteral obstruction and in human CKD kidneys. After IRI, increased *H3K4me3* methylation upregulated expression of inflammatory (TNFα), fibrosis (TGFβ1, type III collagen) and cholesterol-regulated genes 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) that promote transition from AKI-to-CKD [60, 63, 64]. Conversely, inhibiting the synthesis and activation of cholesterol and ATF3 by acetylation of histone residue 9, histone 3 and *H3K4me3*, alleviated kidney injury [65]. Given the role of histone acetylation in AKI-to-CKD transition, the catalytic acetylation enzymes and deacetylation enzymes (HAT and HDAC) are particularly important [66] and are promising therapeutic targets for mitigating AKI-to-CKD transition [60]. In addition, hydroxymethylation of genes like *erythropoietin* and RAS Protein Activator Like 1 (*RASAL1*) promote fibrosis and facilitates the pathogenesis of CKD after AKI [67]. Inducing *RASAL1* demethylation by hydralazine augmented fibrosis in a murine model of IR-induced AKI-to-CKD progression, suggesting its therapeutic potential [60, 68]. Large scale epigenome-wide association studies (EWAS) are instrumental in detecting biomarkers for complex kidney diseases to detect epigenetic modifications [69]. A recent longitudinal EWAS study compared differentially methylated cytosine-phosphate-guanine sites (dmCpGs) in peripheral blood mononuclear cells of kidney transplant recipients pre-transplant and post-transplant. This study identified five dmCpGs including cg23597162 (within JAZF1) and cg17944885, which were found to have associations with CKD in a prior meta-analysis [70, 71].

In addition to epigenetic mechanisms discussed above, noncoding RNAs, mainly microRNA (miRNA) and long noncoding RNA (lncRNA), play pivotal roles in kidney damage and have been studied as potential biomarkers and novel therapeutics for kidney diseases including AKI [72, 73]. Various miRNAs (miR-34b-5p, miR-212, miR-223, miR-140) have been found to promote kidney inflammation in animal models of AKI and are candidate clinical biomarkers of AKI in acute decompensated heart failure patients [72–77].

Proteomics

Proteomics is an "omics" modality that allows the study of composition, structure, expression, modification status and the interactions of large number of proteins. Proteomics technologies evolved rapidly after the completion of human genome sequencing and includes, but is not limited to, mass spectrometry (MS), protein arrays, tissue microarrays (TMA), single cell proteomics, Luminex, Simoa and Olink proteomics [78]. In some ways, studying the proteome of a cell is much more complex than the genome due to constant flux in the protein content of a cell and large number of posttranslational modifications. Proteomics using capillary electrophoresis (CE)/MS, LC/MS and matrix-assisted laser desorption/ionization

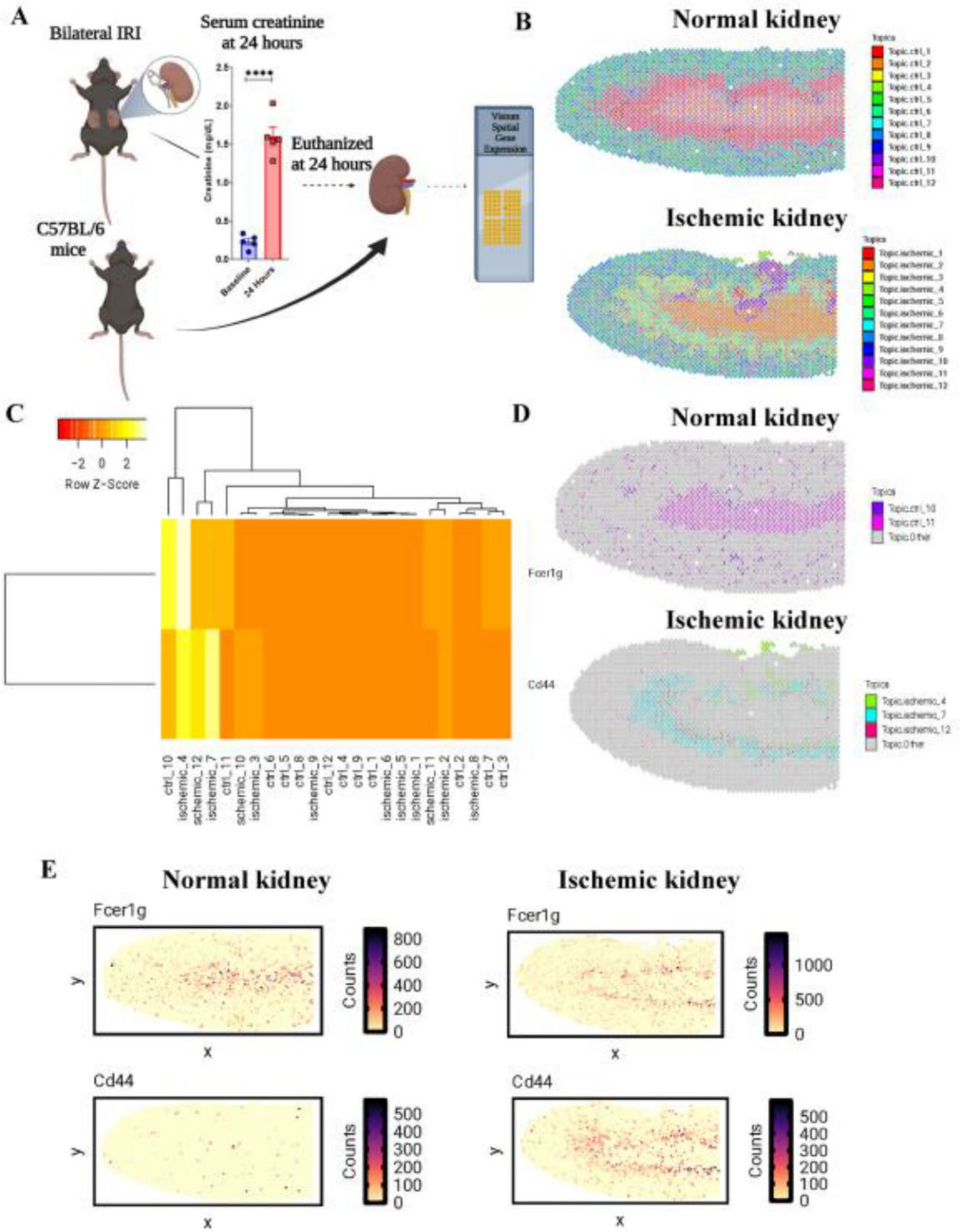

Figure 2: ST in AKI research. ST-based resolution of spatial organization of putative double negative T cells in normal and ischemic kidney samples. 10X Visium workflow generated ST datasets that contains average transcriptional profile for multi-cellular spots tiled across kidney sections. Each spot may be a mixture of multiple cell-types, necessitating deconvolution analysis to recover cell-type specific organization. ST deconvolution algorithms are required to deconvolve these transcriptional profiles to derived putative cell types in each spot. Figure from Gharaie *et al.* 2023 [15].

Table 2: Selected metabolomics studies in AKI.

Disease model	Species	Summary	Reference
IR-AKI	C57BL/6 mice	GC/MS and LC/MS to demonstrate post-AKI changes in kidney metabolome. Changes in specific metabolites were associated with early injury, shift of energy source, inflammation and late-phase kidney recovery	Wei *et al.* 2014 [50]
IR-AKI	C57BL/6 mice	NMR-based metabolomic profiling of mouse kidney, urine and serum at different time points demonstrated sustained metabolomic changes post-AKI	Jouret *et al.* 2016 [51]
UIRI-AKI	Fisher rats	Metabolomics comparison between ischemic and contralateral kidney using NMR and GC/MS showed reduced mitochondrial function in ischemic kidney	Huang *et al.* 2018 [52]
Cisplatin-AKI	C57BL/6 and FVB/N mice	Untargeted metabolomics of plasma, urine and kidney after cisplatin injection found significant alterations in metabolites associated with mitochondrial function, TCA cycle and β-oxidation	Lim *et al.* 2023 [53]
Septic-AKI	SD rats	GC-TOFMS analysis of renal cortex of mice with septic AKI showed altered taurine and hypotaurine, pantothenic acid and CoA biosynthesis, and phenylalanine metabolism	Ping *et al.* 2019 [54]
IR-AKI	C57BL/6 mice	Multi parameter spectral flow cytometry of post-AKI kidney T cells showed reduced voltage-dependent anion channel 1 and mTOR expression. Ischemic kidney also had increased expression of trimethylation of histone H3 lysine 27 and glutaminase	Lee *et al.* 2023 [55]
AKI patients, IRI-induced AKI-to-CKD	Mice and human	For AKI-to-CKD transition, TMAO is a key metabolite associated, and NOX2 is a key regulator for same. Also, the changes in the microbiome can alter TMAO production and improve kidney disease outcomes	Lee *et al.* 2024 [16]
Pre-AKI/AKI patients in PICU	Pediatric patients	Urine metabolite classifier has the ability to identify juvenile populations at risk for AKI, even before the rise of SCr	Franiek *et al.* 2022 [56]
Cardiopulmonary bypass surgery–induced AKI	Piglet	Elevated urine glycolysis intermediates and dysregulated purine and tryptophan catabolism were noted during AKI. In high-risk group, these pathways provide viable targets for postoperative AKI diagnosis and treatment	Davidson *et al.* 2022 [57]
Cardiothoracic surgery–induced AKI	Infants $\leq$120 days old, 57 in number	AKI due to cardiac surgery dysregulates metabolism of purines, cysteines/methionines, with kynurenines/nicotinamides being most significantly impacted. Could serve as possible mechanistic targets to reverse the systemic metabolic effects of AKI and prevent AKI, and for early prediction of severe AKI	Davidson *et al.* 2021 [58]
Contrast-induced AKI	Humans with iodixanol-induced kidney injury	Multiple-metabolites model (leucine, indole, N-acetylvaline, 5-hydroxy-L-tryptophan, hydroxyhexanoycarnitine and kynurenic acid), accurately predicts the early kidney damage and correlates with the degree of renal injury induced by iodixanol	Cheng *et al.* 2022 [59]

PICU, pediatric intensive care unit; UIRI, Unilateral ischemia repurfusion injury.

(MALDI)-MS are being used to develop and characterize novel predictive, diagnostic and prognostic biomarkers from urine that offer better sensitivity and specificity for AKI (Fig. 4) [79]. Urine proteomics studies have found AKI markers including NGAL, which can be used clinically, and novel exploratory biomarkers cystatin C, interleukin-18, albumin [80, 81], tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) (can also be used

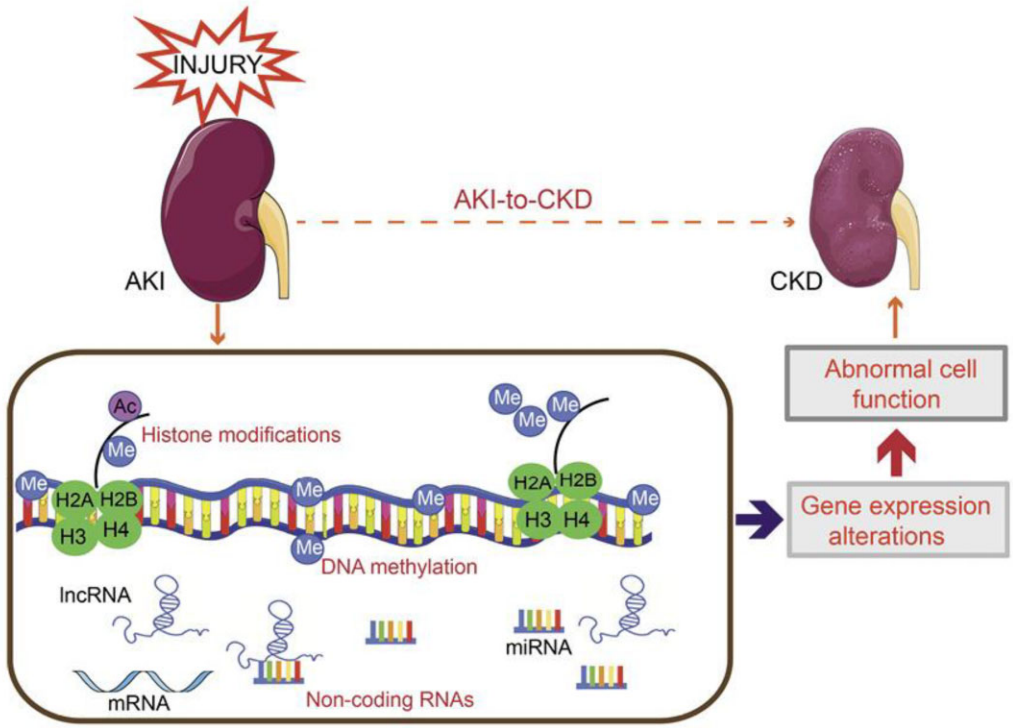

Figure 3: Epigenetic modifications following AKI and effects on AKI-to-CKD progression. AKI can induce epigenetic modification including DNA methylation, histone modifications or changes in noncoding RNAs expression. Epigenetic modifications can have sustained effects on gene expression and cellular function following AKI that promote AKI-to-CKD development. Figure from Li and Li, *Nephron* 2021 [60].

clinically) [81], β_2-microglobulin [82] and urinary transferrin [83, 84] which detect AKI better than serum creatinine (SCr) [85]. LC coupled with Orbitrap Exploris MS and Gemini C18 silica microspheres-mediated peptide enrichment revealed α-1-antitrypsin, β_2-microglobulin and angiotensinogen in cardiac surgery patients with AKI [86]. Proteomic analysis was recently performed on ~4000 urinary proteins in patients with AKI from COVID-19 and identified desmocollin-2, trefoil factor 3 and cystatin C as markers of tubular dysfunction [87]. Furthermore, proteomic and subsequent ELISA-based validation of urinary proteins from pre-term infants with AKI found urinary annexin A5, NGAL and protein S100-P as early and accurate predictors of AKI in pre-term infants [88]. A targeted plasma proteomic characterization found significant correlation between calcitonin related polypeptide alpha (CALCA), calreticulin (CALR), carbonic anhydrase 12 (CA12), C-type lectin domain family 1 member A (CLEC1A), protein tyrosine kinase 7 (PTK7), kidney injury molecule-1 (KIM-1), natriuretic peptide C (NPPC), nucleobindin 2 (NUCB2) and placental growth factor (PGF) with AKI in early sepsis [89]. A recent study used snRNA-Seq and proteomics approaches identified elevated transforming growth factor-β2 (TGFB2), collagen type XXIII-α1 (COL23A1) and X-linked neuroligin 4 (NLGN4X), with decreased plasminogen (PLG), ectonucleotide pyrophosphatase/phosphodiesterase 6 (ENPP6) and protein C (PROC), both in plasma of cardiac surgery and marathon runners, and associated with AKI progression in mouse models [90]. These and several other biomarkers are currently being tested and validated in clinical studies and are expected to greatly improve the accuracy and timing of AKI detection [91–94].

NOVEL IMAGING APPROACHES IN AKI

Imaging provides valuable information about structural, functional and compositional changes once AKI is detected. Several different imaging modalities such as ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) scan are available to gather information on the anatomy of the kidney, to rule out obstruction, to evaluate kidney size, and to obtain information on renal blood flow and kidney function. Ultrasound is the most widely used imaging modality for initial interrogation of AKI. Contrast-enhanced CT and MRI are also used but are limited by the toxicities associated with contrast agents, cost and availability [95, 96]. However, evidence in patients with endovascular thrombectomies [97] and hospitalized children [98, 99] found minimal association between contrast agents and AKI. Recent advancements in ultrasound with improved microbubbles properties and MRI using chemically modified manganese-based labeling as well as nanoparticles have further reduced contrast medium-related adverse kidney effects and allowed assessment of early kidney changes during AKI (Table 3).

Ultrasound

Ultrasound is a noninvasive and simple imaging option that facilitates improved diagnosis and monitoring of AKI (and CKD). Several recent improvements have further enhanced the utility of this technique [100, 101]. Among these, ongoing efforts to improve the microbubble contrast agents is an important development that has boosted sensitivity and specificity of ultrasound for accurately diagnosing kidney diseases. Current im-

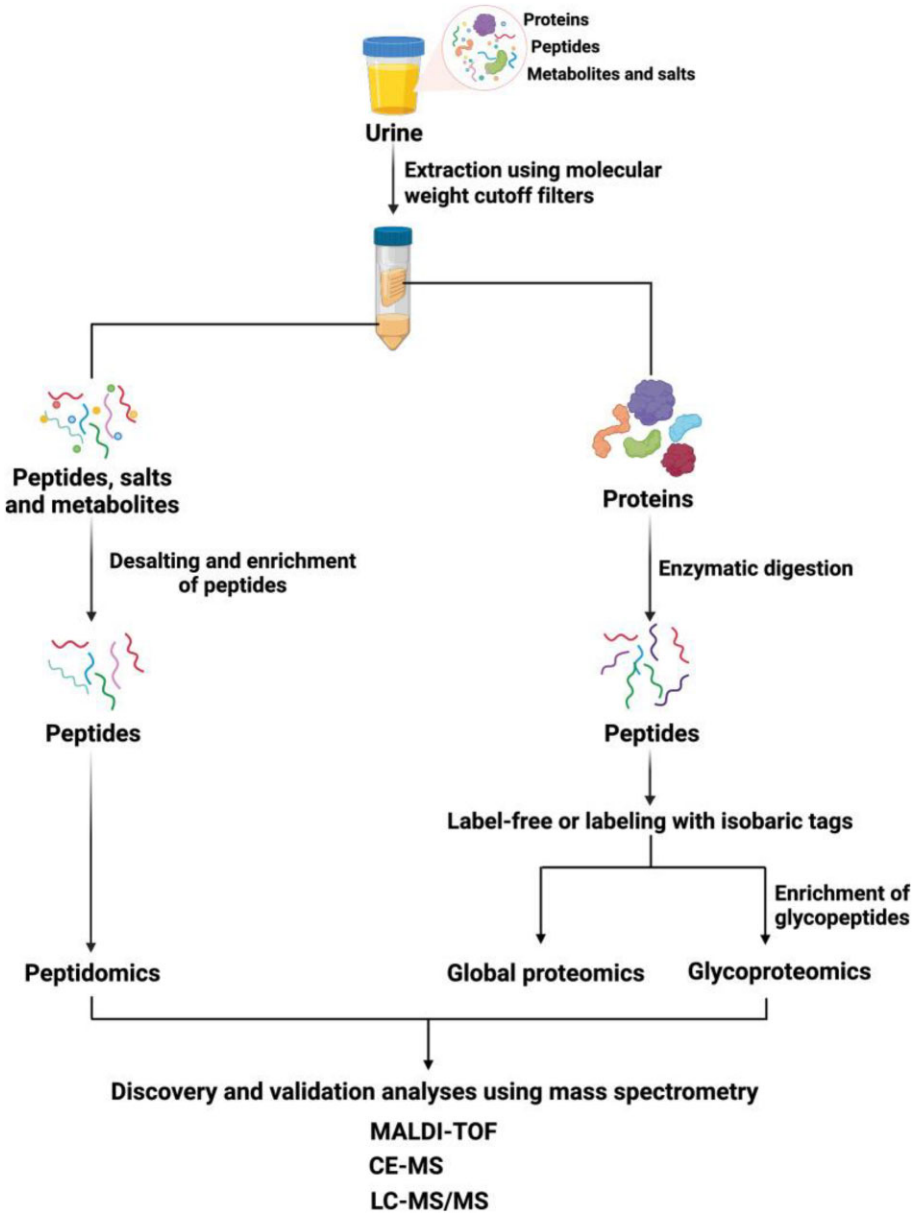

Figure 4: Proteomics approaches in AKI. Schematic showing various steps involved and analytical approaches used for a typical mass spec-based urine proteomics study. The starting material could be urine, plasma or kidney tissue depending on the research question. The workflow shows an example of MS-based proteomic to enrich and study urinary proteins, glycoproteins and peptides. Figure from Joshi *et al.*, *Clin Proteomics* 2024 [79].

provements in microbubbles formulations aim to enhance the echo intensity and mechanical index (MI) tolerance of ultrasound contrast agents. Microbubbles synthesized with reduced graphene oxide from renewable ellagic acid (a non-toxic dietary polyphenol) demonstrated enhanced echo intensity and MI tolerance, which surpassed SoNoVue (SV) microbubbles in *in vivo* studies in normal rat kidneys [102]. Additionally, use of super-resolution ultrasound has been tested to further improve the diagnosis and identification of kidney microvasculature changes during AKI and CKD [103]. A recent preclinical study used super-resolution ultrasound imaging to assess renal vascular alterations and tortuosity (distortion) in type II diabetic rats that showed decreased cortical vascular density in the early phase of diabetic nephropathy and could be a useful tool in AKI [104]. Furthermore, a combination of photoacoustic imaging and ultrasound localization microscopy using microbubbles has been developed to enable super-resolution vascular and physiological imaging of kidneys [105]. An innovative approach demonstrated the potential of contrast agent-free 3D renal ultrafast Doppler imaging that allowed valuable insights into assessing kidney perfusion levels in animal models with significant translational potential for assessing kidneys in diabetic and AKI patients [106]. Interestingly, the stimulation of splenic cholinergic nerve from ultrasound waves has been found to attenuate experimental AKI and prevent CKD by limiting the accumulation of $CD11b^{+}Ly6G^{hi}$ neutrophils and $CD11b^{+}F4/80^{hi}$

Table 3: Select novel imaging approaches in AKI.

Disease	Species, model	Imaging technique	Summary of findings	Reference
Normal	SD rats, no injury	Ultrasound	Reduced graphene oxide with ellagic acid provides high echo intensity and mechanical index tolerance than routinely used ultrasound contrast agents	Cheng *et al.* 2023 [102]
AKI/CKD	C57BL/6 mice, UIRI	Ultrasound	SR-US imaging can identify renal micro vessels with high spatial resolution and potentially aid in diagnosing progressive kidney disease	Chen *et al.* 2020 [103]
AKI	C57BL/6 mice, BIRI	Ultrasound	Ultrasound-based treatment have therapeutic potential for the prevention of AKI by stimulating splenic anti-inflammatory pathway	Gigliotti *et al.* 2013 [107]
AKI	C57BL/6 mice, BIRI	Ultrasound	Ultrasound modulates the splenic neuroimmune axis in attenuating AKI	Gigliotti *et al.* 2015 [108]
AKI/CKD	Rat, UUO	MRI	Mn-based imaging probe Mn-PhDTA allows early detection of kidney dysfunction and analysis of kidney disease progression	Zhang *et al.* 2024 [111]
AKI	SD rat, UIRI	MRI	Mn-CDs can detect early kidney dysfunction and kidney disease progression	Huang *et al.* 2023 [112]
AKI	SD rat, BIRI	MRI	Nanoprobe with self-purification capacity are efficient, targeted and biosafe for CE-MRI of kidney diseases	Zou *et al.* 2024 [113]
AKI	SD rat, BIRI	MRI	SPIO-labeled MSC of the rat in an experimental rat model of AKI feasible in MRI at 3T with a clinically accomplishable imaging protocol	Ittrich *et al.* 2007 [122]
AKI	BALB/c nude mice, cisplatin	*In vivo* imaging system (IVIS) spectrum imaging	Afterglow imaging of Ir-OTf and rubrene nano formulation reliably detects cisplatin-induced kidney injury *in vivo*	Anjong *et al.* 2022 [114]
AKI	Mice/rat, UIRI/gentamycin	IVIS Lumina XR III	Phosphatidylserine targeted and Caspase-3 activatable NIR fluorescence probe (1-DPA2) is suitable for *in vivo* imaging of early AKI	Weng *et al.* 2021 [118]
AKI	C57BL/6J mice	Multiphoton microscopy	Real-time changes in mitochondrial structure and function can be imaged in rodent kidneys *in vivo* using multiphoton excitation of endogenous and exogenous fluorophores in response to ischemia–reperfusion injury or drug toxicity	Hall *et al.* 2013 [120]

UIRI, unilateral ischemia reperfusion injury; BIRI, bilateral ischemia reperfusion injury; UUO, Unilateral ureteral obstruction; SD, Sprague Dawley

myeloid cells in kidney tissue and activating anti-inflammatory mechanisms [107, 108]. Drug-loaded non-toxic microbubbles have been developed and the load release by ultrasound exposure has been shown to be a highly specific treatment modality, making the potential applications of ultrasound even more promising [109, 110].

MRI

MRI is another important non-invasive imaging technique to evaluate kidneys and gather important information on macro- and micro-circulation within the kidney tissue and blood oxygenation/flow. Traditional gadolinium-based contrast agents are contraindicated in patients with AKI, advanced CKD and those receiving dialysis. However, multiple innovative approaches are being employed to reduce contrast agent toxicity and develop novel classes of contrast agents with high sensitivity, improved biocompatibility, high T1 relaxation rate (rate at which net magnetization returns to its initial maximum value) and minimal kidney side effects.

Recently, a small-molecule manganese-based phthalimide tetraacetic acid (Mn-PhDTA) imaging probe has been developed as an alternative to gadolinium-based contrast agents to assess renal insufficiency. Mn-PhDTA provided significant signal

enhancement which enabled distinguishing structural changes between the normal and damaged kidneys, and reliably detected renal function changes at different time points in a unilateral ureteral obstruction (UUO) rat model of AKI [111]. Mn-doped carbon dots (Mn-CDs), which are extremely small (5 nm), improved biocompatibility and T1 relaxation rate during kidney MRI with more clear fine structures of the kidneys up to inner medulla in addition to the cortex and the outer medulla. This study also tested Mn-CDs-based MRI in an AKI model in rats that detected the site of kidney injury consistent with the pathological analysis and reflected the functional changes in the injured kidney [112]. An innovative bioinspired nanoprobe with self-purification capability was developed for enhancing contrast MRI during AKI. The investigators used bovine serum albumin (BSA), polydopamine and iron (Fe) (BPFe) to synthesize nanoprobes with renal tubule-targeting ability, ultra-small size (2.7 nm), excellent solubility, enhanced T1 MRI property and superior biocompatibility. In addition to these improvements, these bioinspired nanoprobes possess a powerful antioxidant capacity against Fe/Mn-based contrast agents that produce significant amounts of reactive oxygen species (ROS). *In vivo* studies using these nanoprobes demonstrated that BPFe nanoprobes accumulated in the renal cortex due to the reabsorption of BSA in the formulation. In the AKI model, impaired renal reabsorption function could be rapidly detected [113].

Emerging imaging techniques

In addition to above-mentioned improvements in ultrasound and contrast-based MRI, several novel innovative imaging technologies have been developed and tested for assessing AKI kidneys in preclinical studies. A recent advance has been the formulation of a multifunctional afterglow nanosensor for *in vivo* molecular imaging of kidneys during AKI. Afterglow is superior to other optical modalities for biomedical imaging since it allows the exclusion of autofluorescence background. A multifunctional iridium complex was studied and recovered its photoactivities upon exposure to superoxide using a nanoscopic afterglow detection system. Using this system, the investigators were able to detect afterglow signals that corelated with overproduced superoxide in a cisplatin-induced AKI mouse model [114]. In a separate approach, kidney clearable near-infrared (NIR) fluorescence probes have been developed for *in vivo* imaging of post-AKI kidneys. Investigators used a renal-clearable ligand, 2-hydroxypropyl-β-cyclodextrin, responsive to several AKI-specific molecules, such as super oxide anion, lysosomal enzyme N-acetyl-β-D-glucosaminidase (NAG), phosphatidylserine and caspase-3. Studies using either single or multiple AKI-specific molecule demonstrated usefulness of NIR probes in predicting AKI due to nephrotoxicity and *in vivo* screening of AKI therapeutics [115–118]. In addition to diagnostics, novel imaging techniques have been utilized for mechanistic understanding of AKI pathophysiology. For example, intravital two-photon imaging has been used to study immune cell behavior and dynamics in the kidney during AKI [119]. Similarly, multiphoton imaging has been used to evaluate changes in mitochondrial structure and function during AKI [120]. Furthermore, bioluminescence imaging has been employed to track *in vivo* distribution of transferred mesenchymal stem cells in an AKI model [121]. MRI using superparamagnetic iron oxide (SPIO)-labeled mesenchymal stem cells [MSC(SPIO)] in kidneys of rats with AKI showed increased kidney volumes and changes in kidney function in MSC-treated animals [122].

Translational utility of novel imaging techniques

The novel emerging imaging techniques discussed above are in various stages of development. Nonetheless, several innovative methods are being evaluated in patients as well [123]. The utility of point-of-care ultrasonography for detecting hydronephrosis was recently demonstrated in a subset of AKI patients [124]. Furthermore, renal contrast-enhanced ultrasonography and multiparametric MRI are considered promising imaging techniques for exploring the pathophysiological mechanisms involved in AKI in critically ill patients [125]. Shear wave elastography, a non-invasive approach that measures stiffness of kidney tissue, has been used to assess AKI in critically ill patients. This study found that patients in the AKI group exhibited significantly increased stiffness in specific kidney regions compared with those in the non-AKI group [126].

NANOMEDICINE FOR AKI

There are no specific therapeutics for AKI except for supportive care. Limitations of candidate therapeutic molecules include high hydrophobicity, low *in vivo* solubility, poor bioavailability and adverse/toxic effects. Nanotherapeutics is an emerging field that is currently being harnessed as a novel treatment strategy for AKI and other diseases, and may ultimately overcome the above-mentioned drug development problems. Current efforts have led to development of different types of nanomaterial, sheets and sponges that primarily scavenge ROS and reduce inflammation in various AKI models (Fig. 5) [127–132].

A recent study used molybdenum-based polyoxometalate nanoclusters as novel nano-antioxidants with preferential renal uptake demonstrated kidney protection in glycerol and cisplatin AKI mouse models [133]. Additionally, mitochondria-targeting ceria nanoparticles with atorvastatin and having recyclable ROS scavenging activity were studied in a sepsis-induced AKI model [134]. Black phosphorus nanosheets have also been tested as nanomedicine agents for ROS scavenging to treat glycerol-induced AKI in mice [135].

Despite these promising results, biosafety of different nanomaterials requires further studies due to their long-term retention in the body. In addition to nanomaterials, extracellular vesicles and micelles are also being developed as novel therapies for AKI [136, 137]. These novel nano-approaches hold significant promise to prevent AKI, accelerate recovery and prevent progression to CKD [132].

ARTIFICIAL INTELLIGENCE IN AKI

Artificial intelligence (AI) is a novel technology that uses machine learning algorithms to analyze big data and recognize patterns, solve problems, and make decisions and judgments in a human-like fashion (Fig. 6). Machine learning is the process by which a computer (machine) trains itself (learning) by analyzing and reanalyzing available/new data to improve, making better decisions and solving problems. The classification of machine learning methods, modeling ideas and evaluation methods, and the characteristics and current status of modeling studies have been systematically reviewed by multiple review articles and will not be discussed here [138–141].

Though AI and machine learning are relatively new, the recent automation of clinical data management and the availability of large amounts of electronic medical records have allowed rapid development of AI and machine learning algorithms for AKI risk estimation [139, 142–144]. Development of machine

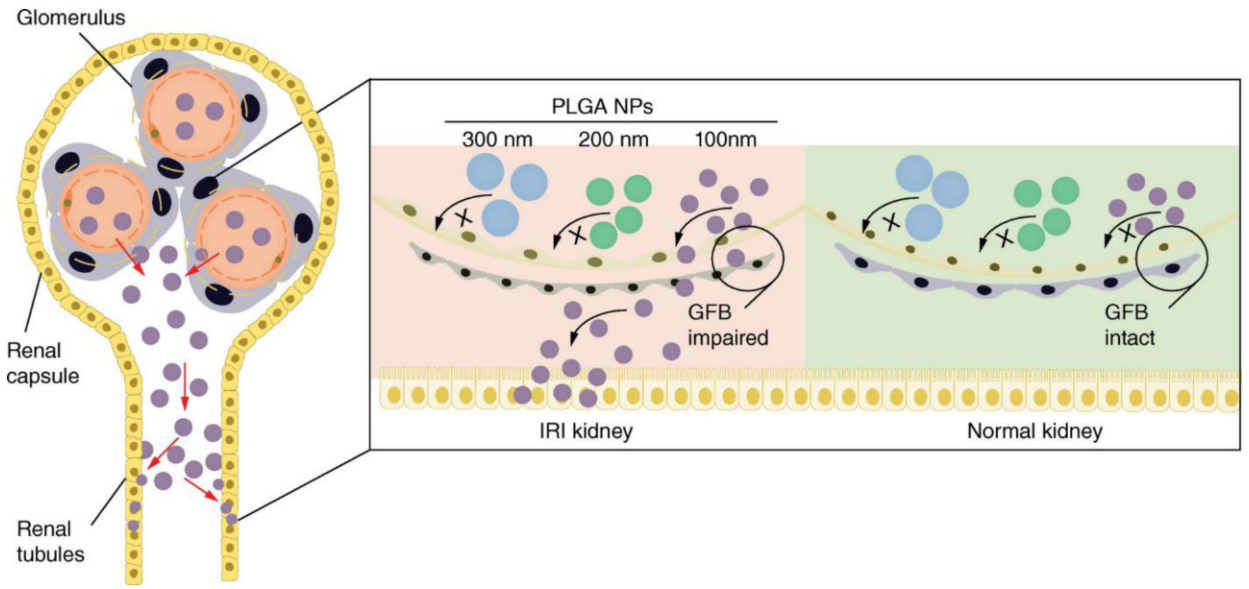

Figure 5: Nanomaterials in AKI. The size of nanomaterials used for AKI therapy are affected by glomerular filtration barrier (GFB) which leads larger nanomaterials to be captured by phagocytic cells thus limiting their accumulation in the kidney tissue. One way to circumvent this problem is to design poly (lactic-co-glycolic acid) (PLGA) nanoparticles. As shown in the magnified inset, 100-nm PLGA-nanoparticles could pass through an impaired GFB after AKI where as in the normal kidney these nanomaterials could not cross GFB. Figure from Li *et al.*, *Nanomedicine (Lond)* 2023 [127].

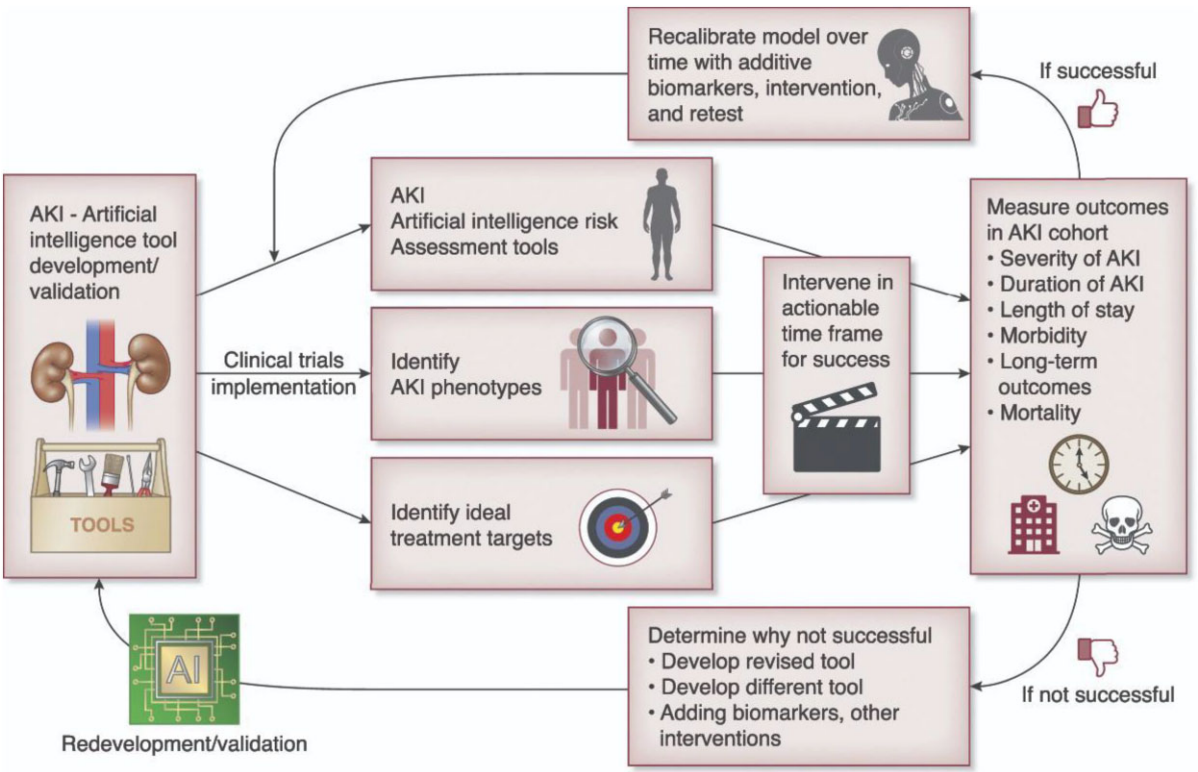

Figure 6: Development and integration of artificial intelligence tools in AKI research. AI tools can be created and evaluated to study risk assessment, phenotyping, and therapy aims. Investigators should be able to quantify a range of clinically significant outcomes related to AKI after a thorough investigation and determination of successful intervention within a feasible time frame by the AI tool. If the model works, it can be used in clinical settings where it can be adjusted and tracked over time to make further improvements the results. Figure used from Bajaj and Koyner, *Clin J Am Soc Nephrol* 2023 [142].

learning algorithms using electronic health records could successfully predict AKI prior to changes in SCr in an observational cohort of hospitalized patients [145]. Machine learning has been used to successfully predict outcomes of AKI in critically ill patients [146, 147]. In an innovative approach, AI was used with Mn-enhanced MRI that was highly sensitive and safe for assessment of kidney injury *in vivo* [148]. Deep learning and neural networks are being developed, tested and refined to interpret and predict imaging and histomorphometry analysis in AKI. A recent study used deep learning algorithm to automate kidney histomorphometric features that demonstrated significant correlation to patient demographics, SCr and eGFR, suggesting that AI based tools can increase the efficiency and rigor of histomorphometric analysis [149]. Addition of new data from diverse populations and various disease stages and novel molecular biomarkers such as urinary KIM-1, liver-type fatty acid binding protein (L-FABP), IGFBP7 and TIMP-2, uromodulin (UMOD) and soluble urokinase plasminogen activator receptor (suPAR) is expected to further improve these AI models [150, 151]. This is particularly important since current AI models are based on traditional serum and urine-based markers which have their own sensitivity and specificity limitations. Additional obstacles that AI must overcome include unequal data quality, lack of established standards across various centers and concerns about data security and privacy [152]. Despite the use of increasingly complex algorithms for AI modeling, clinician involvement is still crucial—for now [153–155].

SUMMARY

In sum, AKI remains a common and serious problem with no specific treatment. Recent and major advances in technologies, some of which have been discussed in this review, hold great promise to help our patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest

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