21 Emerging Therapies: What's on the Horizon?

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21.1 Introduction

Acute kidney injury (AKI) is a multisystem disease with many potential causes. The mortality and morbidity associated with AKI remain unacceptably high despite advances in critical care and dialysis technologies. There is an expanding body of knowledge of the cellular and molecular mechanisms of AKI, which has led to the discovery of many potential therapeutic targets (see Table 21.1). Despite varied triggers, there are certain common features in the renal response to injury. Here we present the data on emerging therapies, potential drug targets and recent negative trials. We have categorized potential therapies according to their site and mode of action (see Figs. 21.1 and 21.2).

21.2 Mitochondria

The renal tubular cells, particularly those that are highly involved in active solute transport, have a rich concentration of mitochondria. Mitochondrial injury has been found to be a common feature of AKI, regardless of the inciting injury. It is an integral component in the pathogenesis of AKI, but may also play a role in promoting kidney injury. Given this, mitochondria are important potential therapeutic targets (see Fig. 21.2). To date, mitochondria-specific pharmacotherapies have largely been prophylactic rather than therapeutic.

21.2.1 Agents Targeting MPTP Opening

21.2.1.1 Cyclosporine

Mitochondrial permeability transition pore (MPTP) is a cyclosporine-sensitive channel located in the inner mitochondrial membrane. In the setting of ischaemia-reperfusion (IR) injury, MPTP opening mediates cell death. Due to its ability to inhibit MPTP opening, cyclosporine A (CsA) has anti-apoptotic properties and may prevent IR-mediated cell injury. A single dose of CsA has also been shown to reduce inflammatory cell infiltration and tubular cell injury [1]. In animal models of IR, the administration of CsA at the time of resuscitation limited the extent of kidney dysfunction [2]. Lemoine et al. recently proposed that the nephroprotective effect of CsA depends on both the dose and the timing of administration, relative to IR injury [3]. Unfortunately, there are distinct disadvantages

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Table 21.1 Summary of potential therapies for the prevention and treatment of AKI

Agent	Site of action	Mechanism of action	Drug development stage	Role in AKI
Cyclosporine	Mitochondria	Inhibition of MPTP opening	Phase 2 underway	Prevention
NIM-811	Mitochondria	Inhibition of MPTP opening	Preclinical	Prevention
Bendavia	Mitochondria	Mitochondrial antioxidant	Phase 2 underway	Prevention and treatment
MitoQ	Mitochondria	Mitochondrial antioxidant	Preclinical	Prevention and treatment
Sildenafil	Mitochondria	Induction of mitochondrial biogenesis	Phase 1 underway	Prevention and treatment
	Vasculature	Local vasodilation		
Mdivi-1	Mitochondria	Inhibition of mitochondrial fission	Preclinical	Prevention
4-Phenylbutyrate	Endoplasmic reticulum	Reduction in expression of CHOP/GADD153	Preclinical	Prevention
EET analogues	Endoplasmic reticulum	Reduce ER oxidative stress	Preclinical	Prevention
Fingolimod	Cell membrane	Activation of S1P receptor	Phase 3	Prevention
Nicotine	Nicotinic receptor	Anti-inflammatory effect	Preclinical	Prevention
Endothelin receptor antagonists	Endothelin receptor	Alteration of renal haemodynamics	Preclinical	Prevention and treatment
OPN-305	Toll-like receptor 2	Inhibition of TLR2-induced initiation of innate immune responses following kidney injury	Phase 2 underway	Prevention
Angiopoietin agonists	Endothelium	Anti-inflammatory effects Enhanced endothelial cell survival	Preclinical	Prevention
Endothelial progenitor cells	Endothelium	Endothelial repair and regeneration	Preclinical	Treatment
QPI-1002	Gene silencing	Temporary suppression of p53 expression	Phase 1/2	Prevention
HMGB1 antagonists	Antisepsis	Anti-inflammatory and anti-apoptotic effects	Preclinical	Prevention
Alkaline phosphatase	Antisepsis	Anti-inflammatory effect through generation of adenosine and phosphorylation of endotoxin	Phase 2	Treatment
Caspase inhibitors	Antisepsis	Anti-inflammatory and anti-apoptotic effects	Preclinical	Prevention
Bone morphogenetic protein 7	Antisepsis	Inhibition of TGFβ signalling Anti-inflammatory and anti-fibrotic effects Downregulation of adhesion molecules	Phase 1	Prevention and treatment
EA-230	Antisepsis	Anti-inflammatory effects Improvement in renal blood flow	Preclinical	Treatment

to the use of cyclosporine as a prophylactic agent for AKI. The potent immunosuppressive and renal vasoconstrictor properties of this drug are likely to limit its clinical utility in the prevention of AKI. A phase II trial exploring the ability of cyclosporine to reduce the risk and degree of AKI in the context of cardiac surgery is underway.

21.2.1.2 Other Cyclophilin Inhibitors

N-Methyl-4-isoleucine cyclosporine (NIM-811) is a non-immunosuppressive cyclophilin inhibitor. NIM-811 has been found to improve kidney dysfunction significantly following IR injury in rabbits [2]. It had comparable efficacy to cyclosporine but without the systemic side effects. Preclinical studies suggest that it may have a role

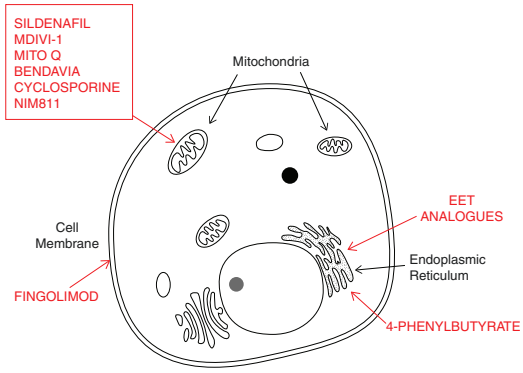

Fig. 21.1 Novel drugs and their target within the renal tubular cell

in preventing irreversible cellular injury. Early clinical trials report a favourable safety profile.

21.2.2 Agents Targeting Mitochondrial Oxidative Damage

21.2.2.1 Mitochondrial-Targeted Antioxidants

Oxidative injury to mitochondria is a prominent feature of IR injury. The inability of damaged mitochondria to recover ATP leads to tubular cell injury and promotes AKI. Most antioxidant

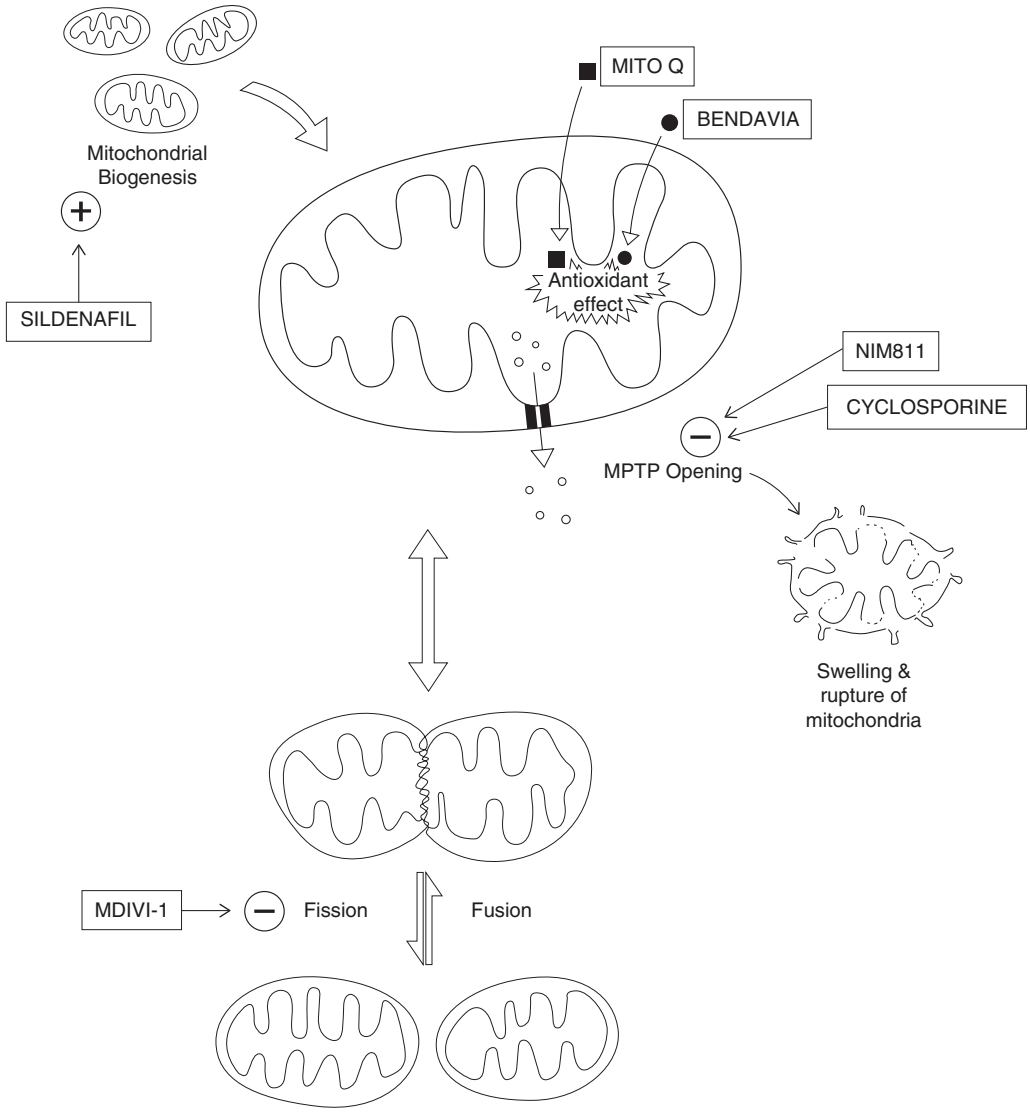

Fig. 21.2 Novel drugs targeting mitochondria and mitochondrial dynamics

agents are clinically ineffective as they are not taken up by mitochondria. Novel mitochondria-specific antioxidants are showing promising results in early clinical trials.

MitoQ is a mitochondria-targeted antioxidant agent that accumulates in mitochondria, localizing within the inner mitochondrial membrane (IMM). Once there, it is continually reduced by the respiratory chain and prevents mitochondrial oxidative damage. It was the first mitochondria-specific antioxidant agent to undergo clinical trials in humans. It has been found to be effective in reducing tubular damage and cell death during cold storage of porcine kidneys [4]. Pretreatment with MitoQ protected mice kidneys from IR-mediated damage and dysfunction [5]. MitoQ has undergone early clinical trials in Parkinson's disease and hepatitis without any serious adverse events [6, 7]. MitoCP, another mitochondria-targeted antioxidant, may have similar protective properties. It has been shown to prevent cisplatin-induced renal dysfunction in mice in a dose-dependent manner [8]. These potent mitochondrial antioxidants hold promise as an effective preventative therapy for AKI.

21.2.2.2 Bendavia

Cardiolipin is a phospholipid, located in the IMM and involved in many essential mitochondrial functions. Ischaemic injury causes peroxidation of cardiolipin through the generation of reactive oxygen species (ROS). Structural and functional defects in the mitochondria occur as a result. The peroxidation of cardiolipin also promotes the dissociation of cytochrome c from the IMM into the cytosol, activating programmed cell death pathways.

Bendavia (SS-31 or MTP-131) is a tetrapeptide that inhibits the peroxidation of cardiolipin [9]. It has been shown to accelerate the recovery of ATP after ischaemic insult and ameliorate kidney injury [10]. Pretreatment of rats with bendavia resulted in improved repair of mitochondrial morphology and reduced tubular apoptosis and necrosis after IR injury. Early studies look promising, and phase 2 trials are underway.

21.2.3 Sildenafil

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), which increases endogenous nitric oxide (NO) activity. The preservation of NO levels has been found to protect the kidney against a range of insults. There is evidence that PDE inhibitors can induce mitochondrial biogenesis, a key step in the recovery of renal function in AKI [11]. Another postulated mechanism for the renoprotective effect of PDE inhibitors is through local vasodilation. In an experimental model of ischaemic kidneys, a more favourable haemodynamic pattern was evident in animals pretreated with sildenafil [12].

Sildenafil may have the potential to accelerate the recovery from AKI in addition to having a prophylactic effect. In animal models, pretreatment with sildenafil has been shown to lessen histological injury, attenuate serum creatinine levels and reduce reactive oxygen species generation [13–15]. Recently, a phase 1 study reported that sildenafil was well-tolerated in cardiac surgery patients [16]. Unfortunately, a randomized placebo controlled trial by Krane et al. did not observe a significant renoprotective effect with a single preoperative dose of sildenafil [17]. The lack of an observed beneficial effect may relate to the dosing regimen used in this study. Sildenafil has a short half-life, and it may be necessary to administer repeated doses for a protective effect. This potential disadvantage of sildenafil could limit its clinical utility.

21.2.4 Mitochondrial Division Inhibitor-1

Mitochondrial dynamics are governed by two key processes: fission and fusion. There is evidence to indicate that proteins involved in mitochondrial fission actively participate in apoptosis. Dynamin-related protein 1 (Drp-1) is an integral

mitochondrial fission protein. Inhibition of Drp-1 inhibits mitochondrial fission and delays programmed cell death.

Mitochondrial division inhibitor-1 (mdivi-1) is a selective inhibitor of Drp-1 that partially inhibits apoptosis [18]. Experimental studies have demonstrated that it can prevent mitochondrial fragmentation and tubular cell apoptosis during kidney injury [19]. However, Sumida et al. did not identify a significant renoprotective effect when they administered mdivi-1 to mice with IR injury [20]. In addition to these inconclusive preclinical results, there is concern that permanent inhibition of mitochondrial fission may have detrimental effects on mitochondrial and cellular function.

21.3 Endoplasmic Reticulum

The endoplasmic reticulum (ER) is a network of tubules within the cytoplasm. ER stress contributes to AKI. Tunicamycin is an antibiotic that induces extensive ER stress and has been shown to induce substantial proximal tubular damage. Many researchers have utilized it to induce ER stress and AKI in animal studies. There is evidence to suggest that males may be more vulnerable to ER stress than females [21], which may partly explain gender differences in the response to renal injury.

21.3.1 4-Phenylbutyrate

C/EBP homologous protein (CHOP) is a protein that mediates ER stress-induced apoptosis. Prolonged ER stress in renal cells results in upregulation of CHOP. The chemical chaperone, 4-phenylbutyrate (4-PBA), reduces the expression of CHOP. In mice with tunicamycin-induced AKI, 4-PBA has been shown to protect the kidney and reduce the extent of tubular injury [15, 22]. It appears to protect the kidney through the inhibition of ER stress. Taurodeoxycholic acid is another chemical chaperone, which appears to protect kidney cells through a similar mechanism [23].

4-PBA is approved for use in urea cycle disorders and has undergone clinical trials in non-renal conditions such as neurodegenerative diseases, liver cirrhosis and certain cancers. It has been reported to have an acceptable safety profile in these conditions. At present, its use in renal diseases has not progressed past preclinical testing. It may prove to be an effective prophylactic agent. Those most likely to benefit are patients at high risk of AKI in which ER stress is a prominent pathogenic feature, e.g. cisplatin- and contrast-induced AKI.

21.3.2 Epoxyeicosatrienoic Acid Analogs

Epoxyeicosatrienoic acids (EETs) are metabolites of arachidonic acid, with anti-inflammatory and antioxidant effects. Also, they have potent vasodilatory and antihypertensive properties. Based on the results of experimental models, EET analogues can protect against organ injury in conditions such as diabetes and cardiovascular disease. They have also been found to protect the kidney from cisplatin-induced apoptosis through various mechanisms. Amongst these mechanisms is its ability to reduce ER stress and attenuate renal inflammation secondary to cisplatin [24]. It accomplishes this without attenuating the chemotherapeutic effects of cisplatin. Unfortunately, EETs may promote tumour growth and metastasis [25, 26]. This concerning finding may limit their clinical utility.

21.4 Cell Membrane

The cell membrane is a primary site of damage in AKI. Both necrosis and apoptosis feature alterations in the cell membrane and both forms of cell death can exist in AKI. The plasma membrane is an exciting potential target for therapies to prevent or attenuate AKI.

Fingolimod Sphingolipids are integral components of the cell membrane. The metabolites of sphingolipids, which include sphingosine-1-phosphate (S1P), act as important signalling molecules. S1P is a ligand for a family of five G-protein-coupled receptors. Through its actions on these receptors, it is involved in many cell processes, including cell growth and the suppression of apoptosis. S1P plays a pivotal role in determining cell fate. Activation of the S1P receptors has been shown to protect the proximal tubular cells from IR injury.

Fingolimod (also known as FTY720) is an orally active immunomodulatory agent that activates the S1P receptor. When administered before IR injury, fingolimod was shown to attenuate kidney injury [27–29]. It has been approved for the treatment of multiple sclerosis in many countries. The results of several phase 3 trials of fingolimod in renal transplant patients are awaited.

21.5 Receptors

Many cell surface receptors have been implicated in epithelial injury, and subsequent repair, in AKI. Signalling through certain receptors (e.g. epidermal growth factor receptor and the hepatocyte growth factor receptor) has a protective or regenerative effect. Others, such as TGF-β, can increase apoptosis. There is scope to attenuate or prevent kidney injury by chemically targeting receptors. Here we outline drugs that have successfully manipulated receptor pathways to protect against and treat AKI in experimental models.

21.5.1 Nicotinic Agonists

The cholinergic pathway has been linked with an anti-inflammatory effect, in particular through activation of the α7 nicotinic receptor (α7nAChR). Nicotine is a directly acting cholinergic agonist that mediates its actions through stimulation of the nicotinic acetylcholine receptors. Although chronic nicotine exposure has been linked with adverse renal effects, nicotine has also been found to have a powerful anti-inflammatory effect. Through α7nAChR-dependent regulation of the immune response, nicotine may limit tubular damage and protect renal function after IR injury [30]. Interestingly, although a single pretreatment dose of nicotine prior to IR injury had a protective effect, repeated administration over several days before injury had the opposite effect in a mouse model of IR injury [31].

Nicotinic agonists may prove to be beneficial in the prevention of AKI. However, it has yet to be determined if the protective effects of nicotine are species-specific. GTS-21 is an agent that selectively stimulates the α7nAChR. It has been shown to reduce the infiltration of leucocytes into the kidney [32]. In animal models, GTS-21 has been found to attenuate renal injury in both IR and sepsis-induced AKI. Due to its selective α7nAChR agonist effects, it may have greater potential as a therapeutic agent for the prevention of AKI. Phase 1 studies have commenced.

Exposure to a modified ultrasound regime has been found to attenuate kidney injury in mice that were subject to IR injury. It is postulated to mediate this effect through its actions on the splenic cholinergic anti-inflammatory pathways, particularly via the α7nAChR [33]. At present, data is limited and is insufficient to propose ultrasound as a prophylactic strategy against AKI.

21.5.2 Endothelin Receptor Antagonists

The kidney is extremely sensitive to endothelin and has abundant endothelin receptors. Endothelin plays an integral role in regulating kidney function through its ability to control global and local renal blood flow. During AKI, there is an imbalance between endothelin and nitric oxide, a potent vasodilator. The effect of endothelin dominates and plays an important role in mediating kidney injury. Through the

endothelin A receptor (ETA), endothelin mediates vasoconstriction of vascular smooth muscle. Through the endothelin B receptor (ETB), it causes vasodilation. While blockade of ETA receptors has been shown to improve renal blood flow, ETB receptor inhibition has been associated with renal vasoconstriction [34, 35].

The administration of non-selective ET receptor antagonists (such as tezosentan and bosentan) before or after IR injury has been shown to protect and optimize kidney function [36, 37]. They have also been found to protect the kidney from renal damage induced by cisplatin and from cardiopulmonary bypass [38, 39]. Although endothelin has been implicated in the progression of AKI to CKD, selective blockade of the ETA receptor did little to prevent the progression of renal injury in mice exposed to unilateral IR injury [92]. Phase 1 and 2 trials looking at the effects of ETA receptor antagonists in chronic kidney disease are underway. Based on experimental studies, the ETA receptor seems to be a likely target for the prevention and early treatment of AKI.

21.5.3 Toll-Like Receptor 2 Antagonists

Toll-like receptors (TLRs) are a family of transmembrane receptors that play a pivotal role in initiating innate immune responses. TLR2 is widely expressed in the kidney and has been implicated in the pathogenesis of AKI. It has been shown to initiate inflammatory responses after kidney injury and is upregulated in renal tubular cells in IR-induced AKI [40, 41]. Blockade of the TLR2 signalling has been shown to reduce neutrophil infiltration and renal damage in an experimental model of IR injury of the kidney [42]. In murine models, the administration of a mouse anti-TLR2 antibody protected transplanted kidneys from IR injury [43].

A humanized monoclonal antibody (OPN-305) that blocks TLR2 signalling has been developed. A phase 2 trial of its efficacy for the prevention of delayed graft function (DGF) in kidney transplant recipients is underway (NCT01794663). There is optimism that it may also prove to be a novel and effective therapy for the prevention of AKI.

21.6 The Endothelium

Renal endothelial cell dysfunction is prominent in the pathogenesis of AKI. IR injury disrupts endothelial cell integrity which consequently influences vascular tone and inflammatory responses. Endothelial cells play a key role in the initiation, progression and recovery phases of renal IR injury. By targeting endothelial cell damage, kidney injury can be partially prevented.

21.6.1 Angiopoietin-1 and TIE2 Agonists

Angiopoietin-1 (Ang1) is an angiogenic factor that acts on endothelial cells through the tyrosine kinase receptor, TIE2. Through its interaction with TIE2, Ang1 plays a role in inflammation and vascular growth and development. It has anti-inflammatory properties and enhances endothelial cell survival.

Ang1 has beneficial effects in AKI. A stable, potent variant of Ang1, COMP-Ang1, has been shown to have a protective effect in lipopolysaccharide-induced AKI [44]. In a model of cyclosporine-induced renal injury, it was shown to protect peritubular capillaries and reduce inflammation [45]. However, in a model of folic acid-induced AKI, although Ang1 was found to stabilize peritubular capillaries, it also demonstrated pro-fibrotic and pro-inflammatory effects [46]. This contrasts with evidence provided by Jung et al., who observed that COMP-Ang1 reduced interstitial fibrosis 30 days after IR injury [47]. It has been postulated that the effects of Ang1 may depend on the disease model tested. The varying effects may also be explained by differences in the potency of Ang1 and COMP-Ang1. Clinical trials in humans are awaited.

21.6.2 Endothelial Progenitor Cells

Endothelial dysfunction and disruption of the vascular barrier integrity are pivotal steps in the pathogenesis of multiorgan failure in septic shock. Endothelial progenitor cells (EPCs) originate in the bone marrow but migrate to the peripheral circulation, where they play a role in endothelial repair and regeneration. In septic shock, the number of EPCs increases, and there is an inverse relationship between EPC numbers and the extent of organ dysfunction. The number of circulating EPCs correlates with survival. In renal ischaemia, EPCs migrate to the renal parenchyma, where they offer partial protection from injury [48]. EPCs may have an important role in ameliorating the effects of AKI. It has been suggested that the renoprotective effects of ischaemic preconditioning may be partially mediated by enhancing the recruitment of EPCs to the renal parenchyma [49].

Stromal cell-derived factor-1 (SDF-1) is a chemokine with regulatory effects on inflammation and cell migration. Through its interaction with the CXCR4 receptor, SDF-1 plays a major role in the recruitment of EPCs to the injured kidney [50]. Theoretically, agonists of SDF-1-CXCR4 should promote the migration of EPCs to the kidney and repair of endothelial cell damage. A high-affinity CXCR4 agonist has been developed, but its effects on kidney injury have not yet been investigated. EPCs and CXCR4 agonists have the potential to play a role in early renal recovery.

21.7 Gene Silencing Therapy

QPI-1002 Apoptosis triggered by p53 activation has been shown to play an important role in the pathogenesis of AKI [51]. QPI-1002 (also called I5NP) is a synthetic small interfering RNA, designed to temporarily suppress expression of the p53 gene. It inhibits p53-mediated apoptosis after kidney injury, allowing kidney cells to repair and regenerate following injury. After administration, QPI-1002 rapidly accumulates within the kidney, with the main site of uptake being the proximal tubular cell [52]. Once the effect of QPI-1002 has subsided, the irreversibly damaged cells undergo apoptosis. A large phase 1/2 trial in kidney transplant patients suggested it could prevent or attenuate delayed graft function in recipients of deceased donor transplants (NCT00802347). An acceptable safety and toxicity profile was reported. Results of a phase 1 study (NCT00554359) in patients undergoing major cardiovascular surgery are awaited. This novel agent is showing promise as a preventative therapy for AKI and DGF in high-risk patients.

21.8 Antisepsis

21.8.1 HMGB1 Antagonists

High-mobility group box 1 protein (HMGB1) is a nuclear protein that bends DNA and acts as a cofactor for gene transcription. It also acts as an extracellular signalling molecule during inflammation. After release from cells undergoing necrosis, HMGB1 activates and propagates the inflammatory response. It has been implicated as an inflammatory mediator in sepsis and IR injury [53, 54]. Through its high affinity binding to the toll-like receptor 4 (TLR4), HMGB1 is also implicated in the pathogenesis of AKI [54, 55].

The blockade of HMGB1 using a neutralizing antibody has been demonstrated to attenuate neutrophil infiltration, tubular necrosis and renal dysfunction in IR injury [55]. Additionally, preconditioning with recombinant HMGB1 has been shown to downregulate the TLR4 signalling in IR injury and protect the kidney [56]. In mouse models of severe sepsis, monoclonal HMGB1 antibodies improved survival from sepsis and reduced circulating levels of pro-inflammatory cytokines [57]. However, the implications of altering the levels of other important cytokines have not yet been explored.

Ethyl pyruvate (EP), an aliphatic ester, has been found to inhibit HMGB1 release. It has anti-inflammatory and antioxidant effects and has been shown to decrease injury in many organs, including the liver, heart and pancreas. In animal models of sepsis, EP reduced circulating levels of HMGB1, attenuated organ dysfunction and

improved survival [58]. In IR injury, EP has been shown to have a nephroprotective effect [59]. Pretreatment of mice with EP resulted in improved short- and long-term kidney function [60]. Phase 1 studies have reported an adequate safety profile. EP and HMGB1 antagonists are potential therapies for sepsis and may have a role in preventing AKI.

21.8.2 Alkaline Phosphatase

Alkaline phosphatase (AP) is showing considerable promise as a treatment for sepsis-associated AKI. There are two proposed mechanisms for this protective effect. AP is an endogenous enzyme that catalyses the conversion of ATP to adenosine, a factor with potent anti-inflammatory and tissue protective effects. It also phosphorylates endotoxins, rendering them non-toxic. When compared with placebo, treatment with bovine AP improved renal function and reduced RRT requirement in patients with severe sepsis [61]. Human recombinant AP (recAP) has been developed, and in animal models of renal IR injury and lipopolysaccharide-induced AKI, it has been shown to exert a renal protective anti-inflammatory effect. A phase 2 trial investigating its efficacy in sepsis-associated AKI has commenced (NCT02182440), and the results will help elucidate if recAP can improve the outcomes of patients with sepsis-associated AKI. This agent may also have protective effects in other forms of AKI.

21.8.3 Caspase Inhibitors

Caspases are a family of intracellular proteases that promote apoptotic cell death and activate pro-inflammatory cytokines. Their ability to trigger, execute and regulate cell death has prompted investigators to explore the potential for caspase inhibition to attenuate organ injury. Caspase inhibitors have been shown to reduce renal damage in animal models of septic, drug-induced and IR-induced AKI [62–65]. The breadth of caspase functionality is being increasingly recognized and so too are the varying roles of individual members of this family. The therapeutic capability of both selective and pancaspase inhibitors is being explored. Pharmacological pancaspase inhibition was well-tolerated by patients with chronic hepatitis C and was shown to reduce markers of hepatocellular injury in a phase 2 trial reported by Shiffman et al. [66]. It seems likely that selective caspase inhibition will yield more predictable clinical effects, compared to pancaspase inhibitors. Human trials of the tolerability and efficacy of selective caspase inhibitors in AKI are awaited. Given the key role these proteases play in programmed cell death, there are grounds for cautious optimism that caspases are novel therapeutic targets for the treatment of AKI.

21.8.4 EA-230

Peptides derived from human chorionic gonadotrophin (hCG) are drawing attention due to the discovery of their potent anti-inflammatory effects. One such peptide is EA-230 (also known as AQGV), a tetrapeptide derived from β[beta] hCG lysates. It has been shown to attenuate multiorgan failure in sepsis and also ameliorates IR-induced kidney injury [67, 68]. In animal models of IR injury, EA-230 was also associated with a substantial survival advantage.

The exact mechanisms of action of EA-230 have not been fully elucidated. It appears to exert an early anti-inflammatory effect on the kidney, thereby preventing organ dysfunction. EA-230 has been shown to reduce neutrophil influx and the release of pro-inflammatory cytokines. It may also improve renal blood flow [69]. Phase 1 trials have been successfully completed and have reported a good safety profile.

21.8.5 Bone Morphogenetic Protein 7 (BMP-7) and THR-184

Bone morphogenetic protein 7, a member of the TGFβ superfamily, plays an important role in nephrogenesis. It may play a role in repair and

regeneration in the adult kidney and has been shown to ameliorate kidney damage through its anti-inflammatory and anti-fibrotic properties. In ischaemic injury to the kidney, BMP-7 inhibits neutrophil accumulation by downregulating the expression of intercellular adhesion molecule (ICAM-1) [70]. In animal models of both obstructive and ischaemic AKI, BMP-7 has been shown to reduce kidney injury and inhibit tubular atrophy [70, 71]. It represents a potential target for the treatment of both AKI and chronic kidney disease.

Due to the high doses required and the expense of production of recombinant BMP, BMP-7 agonists may be a more viable clinical option. Small peptide agonists that bind selectively to BMP receptors have been developed. THR-184 is one such agonist, which activates the BMP signalling pathway. It had a good safety profile in early clinical testing, and a phase 2 clinical trial of THR-184 in AKI has commenced.

21.9 Negative Trials

There is currently no specific therapy approved for the treatment of AKI. Despite optimistic preclinical results, only a small number of drugs have progressed to clinical trials. There are several potential reasons for this (see Table 21.2). AKI is a complex and multisystem disease with a multifaceted pathogenesis. The AKI patient is frequently critically ill with multiple comorbidities. Consequently, a multifaceted approach to treatment is often required. It seems likely that there is a narrow therapeutic window for the treatment of AKI, and an early diagnosis is crucial. The ability to demonstrate the success of therapy partly relies on the early detection of kidney injury. If a rise in creatinine is the trigger for treatment initiation, therapy has probably been commenced too late to show a benefit. Biomarkers of AKI are showing promise and are likely to facilitate the earlier diagnosis of AKI and the development of drugs that can be initiated in a timely fashion.

Table 21.2 Barriers to the development of effective therapies for AKI

The disease	Multiple pathogenic factors
	Many and varied aetiologies
	Multisystem disease
	Timing of diagnosis—need for sensitive biomarkers
The patient	Complex patients, often with multiple comorbidities
	Often critically ill
The trial	Definition and selection of endpoints
	Statistical power
	Translation from "bench to bedside"

Trial design has also acted as a limitation to success in this field. Many studies, particularly those of preventative strategies, have been underpowered. To demonstrate the efficacy of preventative therapy, large numbers of patients are required to ensure a sufficient number of AKI cases. The selection and definition of endpoints can also be problematic. The Acute Dialysis Quality Initiative has endeavoured to reach a consensus regarding AKI staging and diagnosis, which has improved trial design. However, other frequently utilized endpoints such as RRT initiation and mortality also present challenges. In practice, there are substantial differences in the utilization of RRT. A consistent approach is lacking. Trials that select mortality as an endpoint may not be powered to detect small alterations in renal function. We have outlined some of the notable agents that showed initial promise but failed to demonstrate a benefit in clinical trials (see Table 21.3).

21.9.1 Fenoldopam

Fenoldopam is a short-acting α1-selective dopamine agonist that increases renal blood flow even at doses that lower systemic blood pressure. A meta-analysis conducted by Gillies et al. reported that perioperative fenoldopam administration may have the potential to prevent AKI after major surgery [72]. However, mortality and the need for RRT were not attenuated. More recently, Bove et al. reported a decisively negative result [73]. Fenoldopam did not reduce the need for RRT or

Table 21.3 Notable negative trials of agents proposed to prevent or treat AKI

Agent	Negative findings	Reference
Fenoldopam	Did not reduce need for RRT or 30-day mortality compared with placebo	Bove et al. [73]
Alpha melanocyte-stimulating hormone	Did not prevent AKI in patients undergoing high-risk surgery	McCullough et al. [78]
Minocycline	Did not prevent AKI in patients undergoing cardiac surgery	Golestaneh et al. [81]
Statins	Did not prevent AKI in patients undergoing cardiac surgery	Lewicki et al. [82]
Insulin-like growth factor 1	Did not accelerate renal recovery in human trials	Hirschberg et al. [86]
Sodium bicarbonate	Did not prevent AKI in patients undergoing cardiac surgery	Haase et al. [87] McGuinness et al. [88] Kristeller et al. [89]
Balanced crystalloid solution	Did not reduce risk of AKI in critically ill patients	Young et al. [91]
Mesenchymal stem cells	Did not accelerate renal recovery or reduce need for RRT in patients undergoing cardiac surgery	Swaminathan et al. [93]

the 30-day mortality when compared with placebo, but those treated with fenoldopam had a higher rate of hypotension. The trial was terminated for futility.

21.9.2 Alpha Melanocyte-Stimulating Hormone (A[Alpha]MSH)

α[Alpha]MSH is an endogenous anti-inflammatory cytokine that may exert a nephroprotective effect by inhibiting apoptotic and inflammatory pathways [74, 75]. Animal studies of the α[alpha]MSH analogue, AP214 acetate (now known as ABT-719), demonstrated a protective effect in AKI induced by IR injury, sepsis and cisplatin [76, 77]. Unfortunately, this benefit has not been substantiated in human trials. McCullough et al. recently reported on the results of their phase 2b clinical trial of ABT-719 [78]. This agent failed to lower the incidence of AKI in high-risk cardiac surgery patients. Furthermore, it did not attenuate increments in novel biomarkers, nor did it improve clinical outcomes at 90 days.

21.9.3 Minocycline

Minocycline is a second-generation tetracycline antibiotic that has anti-inflammatory and anti-apoptotic effects. The mitochondria appear to be an important site for its protective property. In animal models of IR injury, minocycline was shown to reduce renal inflammation and attenuate renal injury [79, 80]. However, in a clinical trial, minocycline did not protect cardiac surgery patients against AKI [81].

21.9.4 Statins

Statins have been found to have many beneficial effects in addition to their lipid-lowering properties. Amongst these was the implication that they may have a role in preventing AKI by inhibiting inflammatory responses. A recent meta-analysis concluded that the data reviewed do not support the ability of statins to prevent AKI in patients undergoing cardiac surgery [82].

21.9.5 Insulin-Like Growth Factor 1

Insulin-like growth factor-1 (IGF-1) is a polypeptide growth factor with a similar molecular structure to insulin. It has been advocated as an important mediator of renal regeneration in models of AKI. Several preclinical studies have indicated that IGF-1 enhances renal recovery in animals with AKI [83–85].

However, the administration of recombinant human IGF-1 to patients with AKI in a multicentre clinical trial did not accelerate the recovery of renal function [86].

21.9.6 Sodium Bicarbonate

The perioperative administration of sodium bicarbonate initially showed promise as a preventative strategy for AKI post-cardiac surgery. The proposed mechanism of protection was by reducing oxidant damage in the kidney. However, a series of randomized controlled trials have failed to substantiate this [87–89], and in fact, this strategy may increase mortality.

21.9.7 Balanced Crystalloid Solutions

There has been considerable debate regarding the optimal choice of intravenous fluid in critical illness. It has been hypothesized that saline solutions contribute to the development of AKI. Evidence emerged in support of the use of chloride restrictive or "balanced" salt solutions in the prevention of AKI [90]. However, a large randomized trial found that a balanced crystalloid solution did not reduce the risk of AKI when compared with saline [91].

21.9.8 Mesenchymal Stem Cells

Preclinical studies suggested that mesenchymal stem cells (MSCs) had the potential to protect against AKI. Amongst the proposed mechanisms were anti-inflammatory and anti-apoptotic effects. Unfortunately, the beneficial effects of MSC in animal models of AKI have not been replicated in human trials of the disease. A phase 2 trial of mesenchymal stem cell therapy for the prevention of AKI in cardiac surgery patients did not speed up renal recovery or reduce the need for RRT [93].

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