Published in final edited form as:

Pharmacol Ther. 2016 July ; 163: 58–73. doi:10.1016/j.pharmthera.2016.03.015.

Renoprotective Approaches and Strategies in Acute Kidney Injury

Yuan Yang¹, Meifang Song¹, Yu Liu¹, Hong Liu¹, Lin Sun¹, Youming Peng¹, Fuyou Liu^{1,*}, Manjeri A. Venkatachalam², and Zheng Dong^{1,3,*}

¹Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

²Department of Pathology, University of Texas Health Science Center at San Antonio, TX

³Department of Cellular Biology & Anatomy, Medical college of Georgia at Augusta University and Charlie Norwood VA Medical Center, Augusta, GA

Abstract

Acute kidney injury (AKI) is a major renal disease associated with a high mortality rate and increasing prevalence. Decades of research has suggested numerous chemical and biological agents with beneficial effects in AKI. In addition, cell therapy and molecular targeting have been explored for reducing kidney tissue damage and promoting kidney repair or recovery from AKI. Mechanistically, these approaches may mitigate oxidative stress, inflammation, cell death, and mitochondrial and other organellar damage, or activate cytoprotective mechanisms such as autophagy and pro-survival factors. However, none of these findings has been successfully translated into clinical treatment of AKI. In this review, we analyze these findings and propose experimental strategies for the identification of renoprotective agents or methods with clinical potential. Moreover, we propose the consideration of combination therapy by targeting multiple targets in AKI.

Keywords

Acute kidney injury; Kidney protection; Kidney repair; Renoprotection; Ischemia-reperfusion; Nephrotoxicity; Mitochondria; Apoptosis; Reactive oxygen species; Vascular dysfunction; Inflammation

*Corresponding Author: Zheng Dong, PhD, Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China; Department of Cellular Biology and Anatomy, Medical College of Georgia and Charlie Norwood VA Medical Center, 1459 Laney Walker Blvd, Augusta, GA 30912. Phone: (706) 721-2825; Fax: (706) 721-6120; zdong@gru.edu, Fuyou Liu, MD, Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China. lfy2061@163.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declarations

All authors declare that they have no commercial or other conflicting interests.

Introduction

Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of renal function resulting in the accumulation of end products of nitrogen metabolism (urea and creatinine) and/or decreased urine output (KDIGO, 2012). In clinic, AKI occurs mainly as the clinicopathological outcome of renal or extra-renal surgery, bacterial infection, and nephrotoxicity. Large epidemiological studies show a high incidence of AKI in hospitalized patients and in general population (Bellomo et al., 2012; Hsu et al., 2007; Lameire et al., 2013). AKI is considered to be an important independent risk factor for mortality (Uchino et al., 2006). Patients with uncomplicated AKI have a mortality rate of up to 10%. In contrast, patients presenting with AKI and multiorgan failure have been reported to have mortality rates of over 50%. If renal replacement therapy is required, the mortality rate rises further to as high as 80% (Shusterman et al., 1987; Liaño et al., 1998). In addition, AKI is an important factor in the development and progression of chronic kidney disease (CKD) (Chawla et al., 2014; Venkatachalam et al., 2015).

Pathogenetically, AKI is generally described as the injury of renal tubular epithelial cell and vasculature, accompanied by the activation of a robust inflammatory response (Bonventre & Yang, 2011; Molitoris, 2014; Linkermann et al., 2014). In addition, depending on its severity and duration, the damage may spread to glomerulus and interstitium resulting in a full blown, lasting disease. Along with the mechanistic research, a number of agents have been shown for their renoprotective effects in AKI models (Table 1–5), which include some clinical drugs, herbs, active chemicals, hormones, cytokines and growth factors. Moreover, molecular and cell therapies have been attempted with some promising results. In experimental models, these agents and approaches protected kidneys by suppressing inflammation, preserving vasculature, and/or directly preventing tubular cell injury and death (Figure 1). However, up-to-date none of them has been successfully translated to the bedside or the use in patients (Jo et al., 2007). In this review, we have summarized the main renoprotective agents and analyzed their effects in AKI models and relevant mechanisms. We have also discussed the experimental strategies for the discovery of efficacious therapies for AKI, including the use of comorbid models and the test of combination therapies.

I. Chemical Renoprotectants

1. Clinical drugs

Some clinical drugs have been shown to be protective in experimental models of AKI. These include disease-modifying antirheumatic drugs (DMARD), cholesterol-cutting statins, neuroprotective agents for cerebral infarction, selective vitamin D receptor agonist (VDRA), tetracycline antibiotics, phosphodiesterase-5 (PDE5) inhibitors, angiotensin II receptor antagonist, mammalian target of rapamycin (mTOR) inhibitor, immunosuppressant drug, and steroid hormones (Table 1). A notable advantage of clinical drugs is that they have been thoroughly tested for safety in human use and, if effective, they can be relatively rapidly applied for AKI treatment.

1.1 Antirheumatic and statin drugs—Leflunomide is known as an immunomodulating drug for the treatment of chronic inflammatory conditions, such as rheumatoid arthritis. In a

rat model of renal ischemia-reperfusion injury (IRI), leflunomide markedly attenuated renal dysfunction and morphological alterations, and reduced oxidative stress (OS) (Karaman et al., 2006). Similarly, Etanercept (a soluble Tumor necrosis factor- α (TNF- α) receptor) showed anti-inflammatory and anti-apoptotic effects by lowering the expression of TNF- α and monocyte chemotactic protein-1 (MCP-1) in ischemic AKI rats (Choi et al., 2009). For statins, early postoperative statin use was associated with a lower incidence of AKI after cardiac surgery and decreased mortality risk as compared to preoperative statin use or acute statin withdrawal (Molnar et al., 2011; Billings et al., 2010). Several mechanisms have been suggested to contribute to the renoprotective effects of statins in AKI. Statins with their antioxidant, anti-inflammatory and anti-apoptotic effects may protect kidney against gentamicin-, cisplatin- and cyclosporine-induced nephrotoxicity, beyond their lipid-lowering capacity (Dashti-Khavidaki et al., 2013; Kostapanos et al., 2009). They may also block the activation of mitogen-activated protein kinase (MAPK) and the redox-sensitive NF- κ B and activator protein-1 (AP-1) (Gueler et al., 2002). Also statins may ameliorate AKI by directly affecting renal vasculature, an observation that is particularly relevant to sepsis-associated AKI (Yasuda et al., 2006).

1.2 Neuroprotective drugs and Vitamin D receptor agonist—Edaravone is a neuroprotective drug used for treating cerebral infarction through its antioxidant property. In ischemic AKI, edaravone showed renoprotective effects as indicated by decreased serum creatinine (SCr) and blood urea nitrogen (BUN), and increased Bcl-2 expression (Watanabe et al., 2004; Li et al., 2010). Paricalcitol, an agonist of the vitamin D receptor, protected against ischemic AKI by upregulating cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) to attenuate inflammation (Hwang et al., 2013). In line with this observation, Vitamin D deficiency aggravated AKI induced by Tenofovir, a widely used component of antiretroviral regimens for HIV treatment (Canale et al., 2013).

1.3 Inhibitor of phosphodiesterase type 5—Tadalafil and Sildenafil are inhibitors of PDE5, the enzyme responsible for cyclic GMP degradation. Clinically, they are common drugs prescribed for the treatment of erectile dysfunction (ED) and pulmonary hypertension. In ischemic AKI, Tadalafil significantly improved renal function and preserved renal histology, which was associated with the attenuation of AKI biomarkers including kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) (Sohotnik et al., 2013). Similarly, Sildenafil reduced contrast medium-induced AKI in rabbits (Lauver et al., 2014).

1.4 Angiotensin II receptor antagonist and anti-ulcer drug—The angiotensin II receptor antagonist telmisartan was shown to attenuate the increases in BUN, SCr, malondialdehyde (MDA), TNF- α , NO and homocysteine levels in ischemic AKI (Fouad et al., 2010). Consistently, adrenomedullin (AM), a potent endogenous vasodilatory peptide hormone, also delayed the development of contrast-induced nephropathy (CIN) by negative regulation of the renin-angiotensin-aldosterone system (RAAS) (Charles et al., 2003; Inal et al., 2013). Interestingly, the combination of AM with AM binding protein-1 (AMBP-1) could markedly attenuate the inflammatory response in ischemic AKI, suggesting a mechanism of the renoprotective effect of AM (Shah et al., 2010).

1.5 Antibiotics and immunosuppressants—Tetracyclines exhibit significant anti-inflammatory and antiapoptotic properties in AKI induced by hypoxia, azide, cisplatin, or ischemia. For example, minocycline induced accumulation of Bcl-2 in mitochondria and suppression of death-promoting molecules including Bax, Bak, and Bid (Wang et al., 2004), and reduced leukocytes infiltration, leukocyte chemotaxis, and the expression of intercellular adhesion molecule-1 (ICAM-1) (Kelly et al., 2004). Minocycline also reduced renal microvascular leakage which may be related to diminished activity of matrix metalloproteinase 2 (MMP-2) and MMP-9 on the perivascular matrix (Sutton et al., 2005). However, in a clinical study minocycline did not show significant protective effects against AKI that developed post-cardiac bypass surgery (Golestaneh et al., 2015). Doxycycline as another tetracycline antibiotics exhibited renoprotective effects by decreasing levels of IL-1 β , TNF- α and MMP-2 in renal tissue against IRI induced by abdominal compartment syndrome (ACS) (Ihtiyar et al., 2011). Both minocycline and doxycycline were effective in mitigating liver and kidney injury to improve survival in the mouse model of hemorrhagic shock/resuscitation (Kholmukhamedov et al., 2014).

Cyclosporin A, an immunosuppressant drug used in organ transplantation to prevent rejection, blocked the TNF-like weak inducer of apoptosis (TWEAK) expression and NF- κ B activation in folic acid (FA)-induced AKI (Wen et al., 2012). Rituximab is a monoclonal antibody against the protein CD20 used in autoimmune diseases or anti-rejection treatment for organ transplants, which may suppress the inflammation in ischemic AKI (Hwang et al., 2013). In addition, treatment with mycophenolate mofetil together with polyphenolic bioflavonoids reduced tubular damage and attenuated the induction of inflammatory cytokines and renal inflammation (Jones et al., 2000). Thus, anti-inflammation appears to be a common mechanism underlying the renoprotective effects of antibiotics and immunosuppressants in AKI.

1.6 Inhibitors of mammalian target of rapamycin—Mammalian target of rapamycin (mTOR) is a serine/ threonine protein kinase with multiple functions. On one hand, mTOR is a key to cell growth and proliferation by promoting protein synthesis. On the other hand, recent work has demonstrated that mTOR is a crucial, negative regulator of autophagy in response to nutritional status, growth factor and stress signals (Jung et al., 2010; Datta et al., 2014). In AKI, the role of mTOR varies according to experimental models. In ischemic AKI, the inhibition of mTOR by rapamycin impaired or at least delayed kidney repair and recovery by suppressing tubular cell growth and proliferation (Lieberthal et al., 2012). However, in cisplatin nephrotoxic AKI, rapamycin showed protective effects (Jiang et al., 2012). Rapamycin also protected renal tubular cells from apoptosis during ER-stress (Dong et al., 2015). Similarly, rapamycin ameliorated renal injury in diabetic mice and the underlying mechanism may be related to autophagy induction in podocytes (Xiao et al., 2014). In endotoxic AKI induced by lipopolysaccharide (LPS), another mTOR inhibitor Temsirolimus induced autophagy and protected against kidney injury, even after established endotoxemia (Howell et al., 2013). Therefore depending on the models, inhibition of mTOR may protect against or exacerbate AKI. The exact cause of the different effects is unclear, but apparently it results from the multiple functions of mTOR. While mTOR may protect by promoting cell growth and proliferation, it may also enhance injury by inactivating

autophagy. Also it is important to recognize that inhibitors of mTOR (e.g. rapamycin) are immune suppressants that may diminish the inflammatory response in AKI contributing to the observed protective effects of rapamycin in vivo.

1.7 Other clinical drugs—In addition to the drugs described above, several other clinically used drugs have shown renoprotective effects in AKI models. For example, suramin is an antiparasitic drug used for the treatment of trypanosomiasis. Zhuang and colleague demonstrated the beneficial effect of suramin in several kidney disease models, including ischemic AKI and renal fibrosis (Zhuang et al., 2009; Liu et al., 2011). Mechanistically, suramin may promote renal tubular cell proliferation and migration, processes important for kidney repair (Zhuang et al., 2005). Geranylgeranylacetone (GGA), a drug used in the treatment of gastric ulcers, ameliorated ischemic AKI via induction of heat shock protein 70 (Hsp70) (Suzuki et al., 2005). In addition, Fidarestat, an aldose reductase (AR) inhibitor used for treating diabetic complications, protected against LPS-induced endotoxic AKI probably by suppressing the inflammatory response (Kazunori et al., 2012).

2. Renoprotective Chemicals with Clinical Potential

Heme oxygenase-1 (HO-1) and its activators: HO-1 is an inducible enzyme that converts heme into biliverdin and bilirubin, releasing iron and carbon monoxide. The potent cytoprotective role of HO-1 has been recognized for over 20 years (Nath et al., 1992). In kidneys, HO-1 is induced in various AKI models including ischemia-reperfusion, sepsis, and nephrotoxicity (Nath, 2014; Shimizu et al., 2000; Maines et al., 1993). Mechanistically, HO-1 is known to promote the anti-oxidative capacity of the cell. Moreover, it may also dilate blood vessels, increase perfusion, and suppress inflammation in AKI as a result of tissue protection or indirectly by modulating immune cell trafficking (Hull et al., 2015). Several studies have tested the effects of HO-1 induction in AKI. For example, tin chloride (SnCl_2) ameliorated ischemic AKI as shown by the decrease in serum creatinine and BUN and in tubular damage (Toda et al., 2002), while the tin protoporphyrin/ Tin mesoporphyrin/ stannous mesoporphyrin (SnMP, a competitive inhibitor of HO) exacerbated AKI induced by cisplatin (Agarwal et al., 1995; Salom et al., 2007).

Protein kinase C (PKC) inhibitors: PKC is a protein kinase family of multiple members, several of which are induced following renal IR injury in rats (Padanilam, 2001). In a rat model of kidney transplantation, the pan PKC inhibitor sotrastaurin attenuated tubular injury and accelerated renal recovery following transplantation (Fuller et al., 2012). In cisplatin nephrotoxicity, PKC δ was rapidly activated and the inhibition of PKC δ genetically or pharmacologically prevented kidney injury; notably PKC δ inhibitors also enhanced the chemotherapeutic effects of cisplatin in several tumor models, suggesting that blockade of PKC δ may be a “Kill two birds with one stone” strategy in cisplatin chemotherapy (Pabla et al., 2011).

Other renoprotective chemicals: Renoprotective effects have also been shown for the Rho kinase inhibitor Y27632-lysozyme in ischemic AKI (Prakash et al., 2008). Moreover, zafirlukast, the antagonist of cysteinyl leukotriene-1 receptor (CysLT1R, a member of G

protein-coupled receptors superfamily), was shown to alleviate ischemic AKI by reducing neutrophil infiltration as well as P-selectin overexpression in renal tissues (Hanan et al., 2012). Necrostatin-1, a specific inhibitor of the receptor-interacting protein 1 (RIP1) kinase, prevented necrotic cell death and partially preserved renal function during AKI induced by ischemia-reperfusion, contrast media, and cisplatin nephrotoxicity (Linkermann et al., 2013; Linkermann et al., 2012; Xu et al., 2015). In addition, the inhibitor of $\text{Na}^+/\text{Ca}^{2+}$ exchange KB-R7943 may attenuate renal tubular cell death by suppressing the increases of renal endothelin-1 (ET-1) and catalase during ischemic AKI and contrast medium-induced nephrotoxicity (Yamashita et al., 2001; Yang et al., 2013).

II. Herbs, Food and Dietary Nutrients

A variety of herbs, food and dietary nutrients that showed renoprotective effects in AKI models (Table 2).

2.1 Herbs and derivatives

Korean red ginseng is a traditional herbal medicine in China, Korea, and Japan, which was shown to attenuated renal dysfunction, cell apoptosis and tubular damage in cisplatin- and gentamicin-induced AKI mainly by reducing ROS and inflammation (Kim et al., 2014; Lee et al., 2013). Similarly, Radix Codonopsis and the extract saponins increased superoxide dismutase (SOD) level and decreased apoptosis index in a model of kidney transplantation (He et al., 2011), artemisia asiatica extract increased the level of HO-1 and Bcl-2 in the setting of acute renal IRI damage (Jang et al., 2015), and Ginkgo extract (gintonin) was shown to possess anti-oxidation and anti-inflammation activities through suppressing extrinsic apoptotic signal pathway induced by c-Jun N-terminal kinase (JNK) signal pathway (Wang et al., 2008).

Interestingly, some bioactive extracts from herbs, such as flavonoids (naringin, quercetin, curcumin or hesperidin), flavanols (Catechin), Polyphenols (Resveratrol), and Saponin (Astragaloside IV), showed similar renoprotective effects with similar mechanisms. For example, quercetin, naringin, hesperidin, and catechin all reduced lipid peroxidation and restored the levels of antioxidant enzymes SOD and catalase in kidney tissues (Kahraman et al., 2003; Singh et al., 2004; Sahu et al., 2013; Singh et al., 2005). They also showed remarkable anti-inflammation effects (Shoskes, 1998).

Resveratrol is known for its effects on life extension, cancer prevention, and antidiabetic effects (Howitz et al., 2003; Baur et al., 2006; Su et al., 2006). In the animal models of AKI induced by sepsis, IR, glycerol, or cisplatin, Resveratrol improved kidney microcirculation and protected tubular epithelium. Mechanistically, Resveratrol may work by scavenging reactive oxygen/nitrogen species (ROS/RNS), releasing nitric oxide (NO), activating sirtuin 1 (SIRT1) and inhibiting p53 to block apoptosis (Holthoff et al., 2012; Sener et al., 2006; Chander & Chopra, 2006; Kim et al., 2011; Chander & Chopra, 2006). Saponin prevented renal damage through inhibiting ROS and p38 kinase-associated apoptosis pathways in AKI induced by renal IRI or contrast medium (Gui et al., 2013).

2.2 Food and dietary nutrients

Sulforaphane, an organosulfur compound enriched in cruciferous vegetables such as broccoli, protected against ischemic AKI probably by inducing the NF-E2-related factor-2 (Nrf2) antioxidative system (Yoon et al., 2008). Antioxidative activities were also shown for Sesame oil, which was renoprotective during aminoglycoside and iodinated contrast-induced AKI (Hsu et al., 2011; Hsu et al., 2010).

At least two extracts from soybean have been shown to be renoprotective in AKI models. First, polyenylphosphatidylcholine was shown to reduce serum levels of aspartate aminotransferase, BUN and NF- κ B expression (Demirbilek et al., 2006). Second, isoflavone extracted from soybeans protected against ischemic AKI probably by inducing heme oxygenase (Watanabe et al., 2007). In addition, isoflavones, such as daidzein, formononetin, and genistein, may activate the expression of SIRT1 and PGC-1 α to induce mitochondrial biogenesis, leading to accelerated recovery of mitochondrial and cellular functions for renoprotection (Rasbach & Schnellmann, 2008).

III. Antioxidants and Mitochondrial Protectants

Other chemicals with renoprotective effects in AKI include antioxidants and mitochondrial Protectants (Table 3).

3.1 Antioxidants

Oxidant stress is a well-recognized pathogenic factor in AKI. ROS are produced excessively during AKI by several mechanisms. **a.** disruption of mitochondrial homeostasis results in electronic leak from the respiratory chain; **b.** macrophage phagocytosis of cellular debris leads to the release of a large amount of ROS; **c.** hypoxia-reoxygenation in kidney tissues decreases the cellular antioxidant activity (glutathione-GSH, antioxidant enzymes) resulting in redox imbalance (Funk et al., 2012; Samarasinghe et al., 2000; Martins et al., 2003). Consequently, excess ROS in cells induces oxidative damage of proteins, lipid membranes and biological macromolecules, and promotes inflammation and tissue damage.

Glutathione (GSH) is a major cellular antioxidant that is synthesized by the precursors N-acetylcysteine (NAC), glutamine and glycine. NAC showed beneficial effects in various models of AKI and notably, in contrast-induced AKI patients (Kelly et al., 2008). In general, the renoprotective effect of NAC is attributed to improved levels of GSH and associated decrease of ROS in AKI (Duru et al., 2008; Briguori et al., 2011). However, in addition to antioxidation, glutamine may have other effects. For example, it may mitigate renal neutrophil infiltration and tubular cell apoptosis by inhibiting JNK and enhancing Hsp70 (Peng et al., 2013; Kim et al., 2009). Glycine is a classical cell plasma membrane protectant, which protects against kidney tubular cell death by a mechanism related to amino acid gated chloride channels rather than its anti-oxidant activity (Venkatachalam et al., 1996; Sogabe et al., 1996).

In addition, cellular antioxidant enzymes, such as recombinant manganese superoxide dismutase (rMnSOD), reduced OS following contrast medium-induced AKI (Pisani et al.,

2014). Consistently, deletion of extracellular SOD3 led to a more pronounced functional deterioration in AKI, supporting the beneficial effect of SOD (Schneider et al., 2010).

3.2 Mitochondrial protectants

Pathologically, AKI is characterized by tubular cell injury and death. Under this condition, multiple forms of cell death are triggered and mediated by different pathways (Linkermann et al., 2014). Nonetheless, mitochondrial damage appears to be a common factor that induces tubular cell death in AKI. Mitochondrial permeability transition (MPT) at the inner membrane plays a critical role in tubular cell necrosis. As a result, the inhibition of MPT pharmacologically by cyclosporine A or genetically by cyclophilin D ablation led to an increased resistance of kidneys to ischemic AKI (Park et al., 2011; Feldkamp et al., 2009). At the outer membrane of mitochondria, Bax and Bak, two pro-apoptotic members of Bcl-2 family proteins, may co-operate to induce porous defects for the release of apoptotic factors, such as cytochrome c, leading to apoptosis. In ischemic AKI, GSK3 β was suggested to activate Bax via phosphorylation and the pharmacological inhibitor of GSK3 β , TDZD-8, could block Bax activation to afford significant renoprotective effects (Wang et al., 2010). Interestingly, Nutlin-3, an murine double minute-2 (MDM2) inhibitor, was shown to directly antagonize Bax, resulting in the prevention of Bax/Bak oligomerization, inhibition of cytochrome c release, and suppression of apoptosis during cisplatin treatment of renal tubular cells (Jiang et al., 2007). Minocycline, a derivative of tetracycline, may up-regulate Bcl-2 in renal tubular cells to block Bax/Bak activation and apoptosis during hypoxia, ATP-depletion, and cisplatin injury (Wang et al., 2004). These studies support the therapeutic potential of the antagonists of Bax/Bak in AKI.

Mitochondria are highly dynamic organelles that undergo fission and fusion (Brooks & Dong, 2007). In AKI, mitochondrial dynamics is disrupted, resulting in mitochondrial fragmentation, which can be partially prevented by mdivi-1, a mitochondrial fission inhibitor. Importantly, mdivi-1 provided significant protection against AKI (Brooks et al., 2009). This study not only supports a role of mitochondrial dynamics disruption in the pathogenesis of AKI but has also identified a new therapeutic strategy. Mechanistically, it was shown that the fragmented mitochondria are more sensitive to Bax insertion (Brooks et al., 2011). More recent work by Xiao et al has further shown the regulation of mitochondrial fragmentation by inner membrane protease OMA1 cleaving (Optic atrophy 1) OPA1 in ischemic AKI (Xiao et al., 2014).

Several antioxidant agents have been reported to specifically target mitochondria and provide renoprotective effects in AKI. For example, Zorov and colleagues developed SKQR1, a positively charged mitochondrial-targeting compound carrying an antioxidative moiety, which showed renoprotective effects in rat models of ischemic and glycerol-induced AKI (Plotnikov et al., 2011). Mechanistically, SkQR1 may protect by inhibiting MPP and scavenging excessive ROS. Szeto and colleagues have synthesized SS-31, a mitochondria-targeted tetrapeptide with antioxidant property (Szeto et al., 2011). In ischemic AKI, SS-31 protected mitochondrial structure and function, reduced tubular cell death, and partially preserved renal function. Interestingly, the effects of SS-31 may be related to its interaction

with cardiolipin (Birk et al., 2013), a specific type of lipid found in the inner membrane of mitochondria.

In addition to limiting mitochondrial damage, another strategy is to promote mitochondrial biogenesis during and following AKI. In this regard, Schnellmann and colleagues reported that the SIRT1 activator SRT1720 could activate PGC-1 α for mitochondrial biogenesis, leading to the accelerated recovery from ischemic AKI (Funk & Schnellmann, 2013). Their more recent work further demonstrated that formoterol, a potent β 2-adrenergic agonist, induced renal mitochondrial biogenesis and enhanced renal recovery from ischemic injury. Remarkably, formoterol was effective even when given 24 hours after injury (Jesinkey et al., 2014), expanding the time window of treatment of clinical significance.

IV. Hormones with Renoprotective Activities

Several kinds of hormones are known for their protective effects in AKI (Table 4).

4.1 Sex hormones

Several female sex hormones are known to be renoprotective in AKI. 17 β -estradiol (E2), the primary female hormone, is a good example. E2 was shown to protect renal endothelial barrier function in AKI following cardiac arrest and cardiopulmonary resuscitation (Hutchens et al., 2010; Hutchens et al., 2012). Mechanistically, E2 may attenuate renal injury through the activation of phosphatidylinositol-3 kinase (PI3K)/Akt/endothelial nitric oxide synthase (eNOS) pathway (Satake et al., 2008) and by suppressing the renal sympathetic nervous system (SNS) (Tanaka et al., 2012). The pregnancy hormone Relaxin was also protective in AKI and the underlying mechanism may be related to the suppression of TNF- α -related inflammation and apoptosis (Yoshida et al., 2013; Yoshida et al., 2014). Similarly, Oxytocin attenuated ischemic AKI by decreasing TNF- α and oxidative damage (Tu tepe et al., 2007). Renoprotective effect has also been demonstrated for AQGV, an oligopeptide related to the primary structure of human chorionic gonadotropin (beta-hCG), another pregnancy hormone (Khan et al., 2009).

Currently, it is controversial whether the male hormone testosterone/ dihydrotestosterone is good or bad in AKI. Over a decade ago, Park and colleagues suggested a critical role for testosterone in the susceptibility of males to ischemic AKI (Park et al., 2004), and Attia, et al suggested that male gender increases sensitivity to renal injury due to lower renal NOS activity than female rats (Attia et al., 2003). Followup studies have further provided mechanistic insights into the effect of testosterone, referring to decreased expression of histone deacetylase HDAC11 that was accompanied by an increase in PAI-1 expression (Kim et al., 2013). However, a recent study showed a dramatic decrease of serum testosterone during ischemic AKI; further, infusion of testosterone during renal IR protected the kidneys (Soljancic et al., 2013). Interestingly, low dose of testosterone significantly decreased cisplatin-induced nephrotoxicity, while administration of high-dose testosterone enhanced it (Rostami et al., 2014), suggesting a dual role for testosterone at low- or high-doses, respectively.

4.2 Melanocortins

Melanocortins are a group of hormones causing increased pigmentation, which includes alpha-melanocyte-stimulating hormone (α -MSH) and adrenocorticotrophic hormone (ACTH). Star and Colleagues (Chiao et al., 1997) demonstrated the renoprotective effect of α -MSH in ischemic AKI in mice and rats. Mechanistically, although the initial work suggested suppression of neutrophil activation and infiltration in kidneys as a mechanism, a followup study indicated the involvement of neutrophil-independent mechanism (Chiao et al., 1998). AP214, an analogue of α -MSH, was protective in septic and ischemic AKI by reducing NF- κ B activation and splenocyte apoptosis (Doi et al., 2008; Simmons et al., 2010). Somewhat paradoxically, renoprotective effects were also shown for melatonin, the physiological antagonist of α -MSH. It was suggested that melatonin protected kidneys by improving the migration and survival of "early outgrowth" endothelial progenitor cells (eEPCs) (Patschan et al., 2012), a function that is unrelated to that of melanogenesis (Valverde et al., 1995). Moreover the protective effect of α -MSH appears to be AKI model dependent, because it did not ameliorate mercuric chloride (HgCl₂)-induced AKI (Miyaji et al., 2002). Similar to α -MSH, ACTH also demonstrated renoprotective effects in specific AKI models. For example, Gong and colleagues recently showed that ACTH alleviated TNF-induced AKI. Moreover, ACTH appeared to be more efficacious than α -MSH in renoprotection in the septic AKI model of cecal ligation puncture (Si et al., 2013). The beneficial effects of ACTH may derive from both steroid-dependent mechanisms and melanocortin 1 receptor (MC1R)-mediated anti-apoptotic effect.

4.3 Other hormones

Beneficial effects of several other hormones have also been shown in some AKI models. For example, dexamethasone reduced mitochondrial damage, the release of proapoptotic proteins, and the production of pro-inflammatory cytokines in septic AKI following cecal ligation and puncture (Choi et al., 2013). In ischemic AKI, the stomach-derived peptide Ghrelin attenuated the vagus nerve-mediated systemic and kidney-specific inflammatory responses, resulting in significant preservation of renal histology and function (Rajan et al., 2012). Stanniocalcin-1 (STC1) is known as a regulator of calcium and phosphate transport and cellular calcium/phosphate homeostasis (Yeung & Wong, 2011). Sheikh-Hamad and colleagues demonstrated notable renoprotective effects of STC1 in ischemic AKI, which may be related to the induction of mitochondrial uncoupling protein 2 (UCP-2) and suppression of superoxide generation in ischemic AKI (Huang et al., 2012). Their latest work further suggested the activation of AMP-activated protein kinase (AMPK) as an upstream key to the effects of STC1 (Pan et al., 2015). Finally, the neuropeptide pituitary adenylate cyclase activating polypeptide (PACAP) prevented Bcl-2 decrease and apoptosis in ischemic AKI (Horvath et al., 2010), and consistently, PACAP deficiency was associated with an increased susceptibility to ischemic AKI (Szakaly et al., 2011).

V. Cytokines and Growth Factors

5.1 Cytokines

In general, increases of cytokines such as chemokines, TNF- α or ICAM-1 are implicated in the robust inflammatory response observed in AKI. Accordingly, blockade of these

cytokines, their receptors or related signaling reduces inflammation and the associated kidney damage. In this regard, renoprotective effects in AKI have been demonstrated for ICAM-1 monoclonal antibodies, the CXCR₄ (CXC chemokine receptor 4) inhibitor Plerixafor, and the TNF- α inhibitor pentoxifylline (Zuk et al., 2014; Ramesh et al., 2002; Kelly et al., 1996; Kelly et al., 1994).

On the other hand, some other cytokines have notable renoprotective effects. For example, IL-10 is known to inhibit the increases of TNF- α , ICAM-1, and iNOS and protect against ischemic and cisplatin-induced AKI (Deng et al., 2001). In recent work, cardiotrophin-1 (CT-1), a member of the interleukin 6 (IL-6) family, showed significant protective effects in AKI induced by contrast medium (Quiros et al., 2013). In addition, some cytokines may directly protect renal tubules. For example, the lipocalin NGAL inhibited the activation of caspase-3 and reduced Bax expression and renal tubular cell apoptosis in ischemic AKI in rats (An et al., 2013). L-FABP (Liver-type fatty acid-binding proteins) attenuated aristolochic acid-induced nephrotoxicity likely through its antioxidant activity in renal tubules (Matsui et al., 2011). Furthermore, there are cytokines that are beneficial to hemodynamics or angiogenesis in AKI and kidney recovery following AKI. This is well-exemplified by soluble thrombomodulin (sTM) and Cartilage oligomeric matrix protein-angiopoietin-1 (COMP-Ang1), which improved microvascular erythrocyte flow rates and reduced microvascular endothelial leukocyte rolling and attachment during ischemic AKI (Sharfuddin et al., 2009). By improving peritubular capillary and enhancing renal tissue (re)perfusion, these cytokines were shown to alleviate ischemic kidney injury (Kim et al., 2006; Jung et al., 2009).

5.2 Growth factors

Growth factors are signaling molecules between cells that promote cellular proliferation and differentiation by binding to specific receptors on the surface of their target cells. It is known that the activation of growth factor-mediated signaling pathways is important for the survival, migration and proliferation of renal tubular cell during AKI and subsequent renal recovery or repair (He et al., 2013; Tang et al., 2013; Zhou et al., 2013; Mason et al., 2014). In addition, various growth factors including insulin-like growth factor (IGF), epidermal growth factor (EGF), Milk fat globule-epidermal growth factor-factor VIII (MFG-E8), and hepatocyte growth factor (HGF), exerted beneficial effects in models of ischemic-, cisplatin-, HgCl₂-, or glycerol- AKI (Miller et al., 1992; Yasuda et al., 2004; Friedlaender et al., 1995; Matsuda et al., 2011; Yen et al., 2015; Homsy et al., 2009; Chen et al., 2013). These growth factors, when added exogenously, protected against initial injury, enhanced kidney repair and accelerated recovery of renal function. In addition, HGF or IGF-1 expressing mesenchymal stem cells (MSCs) showed a high therapeutic efficacy in ischemic- or cisplatin- AKI models; notably, the efficacy appeared to rely on the growth factor expression on these cells, providing further support for the therapeutic potential of specific growth factors (Imberti et al., 2007; Chen et al., 2011).

Renoprotective effects of haematopoietic growth factors in AKI have also been reported. Especially, Erythropoietin (EPO), named for its function of stimulating red blood cell generation, has been shown to protect against AKI in several models. The tissue protective

effect of EPO appears to be largely independent on red blood cell production; instead, EPO may inhibit cell death and promote cellular repair and regeneration (Sharples & Yaqoob, 2006; Moore & Bellomo, 2011). In addition, granulocyte colony-stimulating factor (G-CSF) has been shown to ameliorate rhabdomyolysis-associated AKI, and interestingly the protective effect may be mediated by the induction of HO-1 (Wei et al., 2011).

However, it is important to note that adverse effects of growth factors have also been reported. For example, IGF-1 enhanced the inflammatory response as indicated by increased neutrophil filtration in a rat model of ischemic AKI, which was associated with higher mortality rate (Fernández et al., 2001). More recently, it was shown that erlotinib (selective EGFR tyrosine kinase inhibitor) partially prevented cisplatin-induced AKI in rats, implying an injurious role for EGFR signaling (Wada et al., 2014). In addition, in post-AKI kidneys, growth factors may promote renal fibrosis. For example, EGFR mutant mice showed more severe AKI following renal ischemia (consistent with a protective role of EGFR signaling in acute injury), but these mice developed less interstitial fibrosis 28 days later, suggesting a role of EGFR signaling in renal fibrogenesis (Tang et al., 2013). Thus, in terms of AKI, the role played by a growth factor or its receptor-mediated signaling may depend on where and when the pathway is activated. This critical question requires detailed research using inducible, tissue-specific conditional gene knockout models (Chen et al., 2012).

VI. Agents targeting gene expression

6.1 Transcription factors

AKI is associated with a significant change in gene expression profile. Thus, it is not surprising that a number of transcription factors may participate in tissue injury as well as protection and repair. Here nuclear factor kappa B (NF- κ B) and hypoxia inducible factors (HIF) are briefly discussed as examples.

NF- κ B is well-known as an inflammation promoting transcription factor that contributes to immune cell infiltration and cytokine production in AKI. In 2004, Cao and colleagues reported that transfection of NF- κ B decoy oligodeoxynucleotides abolished NF- κ B activation in ischemic AKI, resulting in decreases in MCP-1 and ICAM-1 expression, suppression of monocyte/ macrophage infiltration, and significant attenuation of tissue damage (Cao et al., 2004). Consistently, NF- κ B activation was inhibited by pharmacologic agents such as milrinone and resveratrol or overexpression of SIRT1, resulting in a better preservation of renal histology and function in ischemic-AKI and cisplatin nephrotoxic (Jung et al., 2014; Jung et al., 2012). Blockade of NF- κ B was also implicated in the protective effect of Nrf2 signaling (Jiang et al., 2014).

In contrast to NF- κ B, HIF are generally regarded as protective transcription factors in AKI. There are at least 3 members in the HIF family, i.e., HIF-1, -2, and -3. Functional HIF is a heterodimer protein consisting of α and β subunits. In response to hypoxia, HIF- α is stabilized and then associates with HIF- β to translocate into the nucleus to induce the transcription of target genes (Semenza, 2014). HIF-1 plays a pivotal role in the regulation of renal physiology and patho-physiology (Haase, 2013). Pharmacological as well as genetic up-regulation of HIF afforded renoprotective effects in ischemic and nephrotoxic AKI

models (Matsumoto et al., 2003; Weidemann et al., 2008; Hill et al., 2008; Föhling et al., 2013; Conde et al., 2012), suggesting a therapeutic potential. The protective effect of HIF may involve the expression of genes for oxygen delivery, cell survival, and metabolic adaptation. It is noteworthy that HIF may function in different cell types in kidneys: while HIF-1 was generally believed to be the key HIF for renoprotection, recent work by Kapitsinou and colleague however suggests that HIF-2 of endothelial cells may be mainly responsible for the observed protective effects (Kapitsinou et al., 2014). From the point of therapeutics, it is important to note that HIF is also a critical factor for renal fibrosis following AKI (Kapitsinou et al., 2012), it is therefore critical to time the treatment to maximize the protective effect and minimize the fibrogenic effect.

6.2 microRNAs

MicroRNAs are endogenously produced, small RNA molecules that negatively regulate target gene expression mainly by blocking their translation. Recent work has demonstrated the important roles played by microRNAs in renal development, physiology, and pathogenesis of various kidney diseases (Trionfini et al., 2015; Chung & Lan, 2015; Badal & Danesh, 2015; Marrone & Ho, 2014). The role of microRNAs in AKI was first demonstrated by using a conditional knockout model in which Dicer, a key enzyme for microRNA biogenesis, was ablated specifically from renal proximal tubules in mice. In this model, microRNAs were largely depleted from kidney tissues and remarkably, the animals were resistant to ischemic AKI (Wei et al., 2010). By microarray analysis, 13 microRNAs were shown to be significantly up- or down-regulated during ischemic AKI and the latest work has begun to delineate the regulations of these microRNAs and determine their pathological roles. For example, microRNA-687 was shown to be induced dramatically via HIF-1 in ischemic AKI and, upon induction, this microRNA targets phosphatase and tensin homolog (PTEN) to mediate tubular cell death and renal tissue damage (Bhatt et al., 2015). Interestingly, the microRNA expression profiles of bilateral ischemic AKI (Wei et al., 2010) was quite different from that of unilateral ischemia (Godwin et al., 2010), suggesting the sensitivity of microRNA expression. In cisplatin nephrotoxicity, microRNA-34a was shown to be induced via p53 and contributed to cell survival because antagonism of miR-34a with specific antisense oligonucleotides increased cell death during cisplatin treatment (Bhatt et al., 2010). In addition to these earlier studies, more recent studies have further identified miR-24, miR-127, miR-687, and miR-126 as critical regulators of ischemic AKI. For example, Lorenzen and colleagues demonstrated that the silencing of miR-24 ameliorated apoptotic responses and histologic tubular damage in ischemic AKI, resulting in a significant improvement in survival and kidney function (Lorenzen et al., 2014). Also as alluded above, blockade of miR-687 also protected against ischemic AKI (Bhatt et al., 2015). While the induction of some microRNAs have also been reported as beneficial in AKI. For example, miR-127 was shown to protect against ischemic AKI by targeting kinesin family member 3B (KIF3B), which is involved in the regulation of cell-matrix and cell-cell adhesion maintenance (Aguado-Fraile et al., 2012). In cisplatin nephrotoxicity, miR-34a appeared to promote renal tubular cell survival. Consistently, miR-155-deficient mice demonstrated heightened kidney toxicity following cisplatin treatment, supporting a protective role of this microRNA (Pellegrini et al., 2014). The recent work by Bijkerk and colleagues further suggested that overexpression of miR-126 in the hematopoietic

compartment can facilitate vascular regeneration and renal recovery from AKI likely by mobilizing and homing hematopoietic stem and progenitor cells (Bijkerk et al., 2014). Thus, some microRNAs are protective whereas others being injurious in AKI, and targeting of specific microRNAs may offer an effective strategy for the treatment of AKI.

6.3 Epigenetic regulators

A new development in AKI research is the recognition of the involvement of epigenetic regulation in kidney injury and subsequent recovery or repair (Tang, Dong, 2015; Tang, Zhuang, 2015). Epigenetics refers to heritable mechanisms that alter gene expression without changing DNA sequence. DNA methylation and post-translation histone modifications (e.g. acetylation) are major epigenetic mechanisms that may keep the chromatin in an 'open' or 'closed' configuration to facilitate or block gene expression. The earliest evidence for the contribution of epigenetic regulation in AKI came from the study of the effects of the inhibitors of histone deacetylase (HDAC). In 2008, we reported that two HDAC inhibitors, suberoylanilide hydroxamic acid and Trichostatin A, were toxic to renal tubular cells at relatively high concentrations (Dong et al., 2008), but at lower dosages they were protective against cisplatin-induced apoptosis in these cells (Dong et al., 2010). These studies suggested the involvement of epigenetic regulation in AKI and notably, the effect of HDAC inhibitors depended on their dosages. Consistently, MS-275 (another HDAC inhibitor) worsened AKI and prevented kidney repair in the mouse models of AKI induced by folic acid or rhabdomyolysis (Tang et al., 2014), whereas Trichostatin A and methyl-4-(phenylthio)butanoate were recently shown to be beneficial to ischemic AKI (Levine et al., 2015; Cianciolo et al., 2013). Thus, the effects of HDAC inhibitors depend on their specificity, dosages of use, and AKI models of test. Regardless, these studies support a role of epigenetic regulation in AKI and kidney repair following AKI. Recent studies have begun to delineate the specific epigenetic mechanisms in AKI. For example, Bomsztyk and colleagues have recently provided comprehensive information about the epigenetic modifications of histones in mouse models of AKI induced by renal ischemia/reperfusion and lipopolysaccharide (Mar et al., 2015). Further investigation in this area is expected to reveal specific epigenetic mechanisms that may provide effective therapeutic targets for AKI.

A partial list of cytokines, growth factors and proteins with renoprotective effects in AKI is provided in Table 5.

VII. Cell Therapy

7.1 Stem cells

Depending on their differentiation potentials, bone marrow derived stem cells (BMSC) are classified into hematopoietic stem cells (HSCs) and MSCs. BMSC showed renoprotective effects in different AKI models in numerous studies. Earlier studies suggested that BMSC may differentiate into renal tubules for kidney repair after AKI (Kale et al., 2003). But later studies indicated that differentiation of BMSC into renal tubular cells for repair, if any, is a very rare event (Li et al., 2007; Duffield et al., 2005). In these studies, the protective effects were mainly attributable to Mesenchymal stem cells (MSCs/BM-MSCs) (Tögel &

Westenfelder, 2010; Morigi & Benigni, 2013; Fleig & Humphreys, 2014). As alluded above, rather than differentiation into renal tubular cells, MSCs home to the injury sites and mainly function by producing paracrine factors that limit injury in renal tubules in AKI and/or facilitate the kidney repair. For example, knockdown of IGF-1 in MSCs led to a marked reduction of the cells' protective ability in cisplatin-induced AKI (Imberti et al., 2007). Similarly, knockdown of VEGF in MSCs significantly reduced their efficacy in protection against ischemic AKI in rats (Tögel et al., 2009). Interestingly, Hu and colleagues further reported that MSCs mainly accumulated in lung and spleen, and their renoprotective effect in AKI may be related to the induction of T regulatory cells (Hu et al., 2013), suggesting a renoprotective mechanism for MSCs from distant organs, especially the spleen.

In addition to bone marrow, MSCs derived from other tissues also showed the beneficial effects on AKI. For example, the Wharton's jelly-derived mesenchymal stromal cells (WJ-MSC) improved renal function following renal ischemia, which was associated with a stronger proliferative response, less apoptosis and less fibrotic lesions and HGF may be an important contributor to the effects of WJ-MSC (Du et al., 2012). Similarly, adipose tissue-derived MSCs ameliorated folic acid- and cisplatin-induced AKI by producing HGF, VEGF and other factors (Katsuno et al., 2013; Yasuda et al., 2012).

In addition to MSCs, recent work has demonstrated the beneficial effect of the exosomes derived from MSCs in AKI induced by ischemia and cisplatin (Gatti et al., 2011; Bruno et al., 2012). Exosomes, containing specific proteins, mRNAs and microRNAs, are released from various cells and can fuse with neighboring cells to deliver their contents as a means of communication or supplementation. Thus, the exosomes from MSCs may offer a more efficient way to getting access to injured renal tubules for protection and kidney repair.

Obviously, a focus of future investigation is to optimize the condition of MSCs or exosomes derived there from for therapeutic use. In this regard, several bioactive agents have been reported to enhance the renoprotective effects of MSCs. For example, Mias and colleagues reported that melatonin pretreatment could significantly increase the survival of MSCs, their paracrine activity of producing HGF and FGF, and the beneficial effect of MSCs in ischemic kidney (Mias et al., 2008). Genetic modification of MSCs is another option to improve the efficacy of renoprotection. For example, overexpression of CXCR4 (the alpha-chemokine receptor specific for SDF-1/CXCL12) improved the reparative ability of MSCs in AKI by enhancing their homing to injured kidneys and production of cytokines such as BMP-7, HGF, and IL-10 (Liu et al., 2013).

7.2 Endothelial progenitor cells

EPCs are bone marrow-derived, circulating progenitor cells of the endothelial lineage (Asahara et al., 1997). Interestingly, patients suffering from sepsis-induced AKI showed a significantly higher level of circulating EPCs (Patschan et al., 2011). In AKI, microvascular endothelial cell dysfunction results in a decline of perfusion in peritubular capillaries, leading to the suppression of kidney repair or recovery. In 2006, Patschan and colleagues (Patschan et al., 2006) demonstrated the mobilization and homing of EPCs to injured kidneys in ischemic AKI. Importantly, transplantation or systemic administration of EPCs afforded renoprotective effect (Patschan et al., 2010). Interestingly, Li and colleagues

showed that prior induction of hematopoietic stem and progenitor cells (HSPC) before application may provide a better protection by producing renoprotective factors including VEGF, IGF-1, and HGF that promote epithelial proliferation and tubular repair (Li et al., 2012). Similarly to that of MSCs, microvesicles or exosomes derived from EPCs were shown to attenuate ischemic AKI, notably, by harboring endothelial-protective miRNAs such as miR-126 and microRNA-dependent reprogramming of resident renal cells (Bitzer et al., 2012).

7.3 T lymphocytes

In addition to their well-recognized injurious role, research in recent years has established a protective role for specific subsets of lymphocytes (Jang et al., 2015). Especially, the depletion of T_H17(+)CD4(+)CD25(+)Foxp3(+) regulatory T cells (Tregs) after ischemic injury led to enhanced pro-inflammatory cytokines production, increased renal tubular damage, and reduced tubular proliferation, while infusion of Tregs enhanced kidney repair and recovery (Gandolfo et al., 2009; Kinsey et al., 2009). These and other follow-up studies indicate that the pathological role of T cells in AKI depends on the cell subtype and the stage of injury. How to specifically stimulate Tregs for renoprotection? Lai and colleagues identified the potential in N, N-dimethylsphingosine (DMS), a naturally occurring sphingosine derivative and sphingosine kinase inhibitor. DMS was shown to recruit Tregs and protect against ischemic AKI; notably, the protective effect of DMS was abolished when Tregs were depleted (Lai et al., 2012), suggesting that DMS protects kidneys by recruiting Tregs. Research in this direction may lead to the development of therapeutic agents for clinical application, whereas cell therapy using Tregs may be technically more challenging.

VIII. Final thoughts on the strategies for identifying renoprotective agents

As discussed, numerous agents and approaches have been reported to be effective in protecting against AKI in experimental models. However, most have yet to enter clinical trial (Faubel et al., 2012). For those tested in patients, none has been successfully translated into clinical use. The reason can be many, including the complexity of the pathogenesis of AKI, the heterogeneity of the patients, and the defects in the design of previous clinical trials, just to name a few. On the bench side, it is crucial to thoroughly verify the effects of potential protective agents before considering or proposing clinical tests. The verification needs to cross-checked against multiple AKI models and also considers comorbid factors.

Currently, mouse and rat models are most commonly used for AKI research and for the test of potential renoprotective agents. Compared to mammals, the rodent models have notable merits, including the feasibility of transgenics. However, rodents are known to have major differences in the structural organization of kidneys. Especially, compared to mammals (e.g. dog), rodents have a relatively thicker renal medulla and a more complex vasculature that leads to the unique feature of “non-reflow” following ischemic injury. As such, many renoprotective agents shown in rodent ischemic models may fail in the models of higher animals since those agents mainly target the “non-reflow” phenomenon. Thus, it is important to verify the effect in rodent experiments by using higher animals, such as pig, dog, or sheep (Figure 2).

Clinically, there are various causes of AKI, which may be broadly divided into sepsis, nephrotoxicity, and renal ischemia-reperfusion. It is noteworthy that these causes are not mutually exclusive and in many cases, they co-exist. For example, ischemic injury may be an important component in nephrotoxic AKI due to toxic damage of vasculature and ensuing ischemia in kidney tissues. Importantly, while the cause of AKI is known for some patients (e.g. renal ischemia following cardiac surgery or nephrotoxicity after cisplatin chemotherapy), the cause of AKI for the majority of patients is unclear at admission. Under these conditions, it would be ideal to have a treatment that has a broad therapeutic spectrum. To discover such therapies, it is necessary to examine the effect in AKI models of different pathogenic origins (Figure 3). If the renoprotective effect of an agent is verified in two or more models, the chance of success in clinical trials is higher.

In addition, it is well recognized that AKI in young and otherwise healthy patients is mostly completely reversible. However, in clinic settings, a large portion of AKI patients also suffer from comorbid conditions, such as diabetes, hypertension, CKD, and/or aging. It is in this population of patients that AKI is severe, hard to recover, and likely to progress into end-stage renal disease or chronic kidney disease. Unfortunately, most previous studies investigated AKI in young and healthy adult animals without considering the comorbid factors that are known to have profound effects on the outcome in AKI patients. In this regard, AKI in aging has been studied for years (Rosner, 2013; Wang et al., 2014). Moreover, recent studies have begun to test comorbid models. For example, cisplatin nephrotoxicity has been investigated in tumor-bearing animal models (Pabla et al., 2011; Oh et al., 2014). and ischemic AKI examined in diabetic animals (Kelly et al., 2009; Peng et al., 2015; Gao et al., 2013). The comorbid models are obviously more complex; however, they are also more relevant to the patient condition and, as a result, renoprotective agents identified from these models are more likely to succeed at the bedside (Figure 4).

Finally, depending on the etiology, AKI is mostly a combined result of the damage and dysfunction in kidney parenchymal and mesenchymal tissues, especially renal tubules, vasculatures, and immune response and inflammation. In view of such a complex pathogenesis, it is hard to envision a “silver bullet” for its optimal treatment. Rather, less specific, “dirty” drugs with multiple targets might be more effective. In this regard, cell therapy may be a good example. In addition, it is also important to consider the strategy of combination therapy, which takes advantage of the differential renoprotective effects of two or more agents. As presented in this review, various classes of renoprotective agents, including clinical drugs, herbs, natural or synthetic chemicals, bio-active proteins or peptides, and stem cells, have been described (Table 1–5). Notably, these agents have multiple and diverse mechanisms of protection, ranging from anti-oxidation, anti-inflammation, anti-apoptosis, and mitochondrial protection, to the activation of autophagy and other pro-survival pathways (Figure 1). Can the agents be used in combination to achieve better protective effects? Theoretically it is plausible. For example, it seems logical to combine a renal tubule protectant with an anti-inflammatory agent. However, the idea of combination therapy has rarely been tested, even in animal models (Liu et al., 2013).

In summary, decades of research has gained significant insights into the pathogenesis of AKI. Along the research, various renoprotective agents have been identified. Further

investigation may cross-check their efficacy in multiple AKI models and also in comorbid models containing comorbid factors. Moreover, therapeutic efficacy may be improved or optimized by combination therapies.

Acknowledgments

This study was supported in part by grants from the National Natural Science Foundation of China (81430017), the Hunan Province Natural Science Foundation, China (No.2009TP-1066-2), the National Basic Research Program of China 973, program No. 2012CB517601, the scientific research project of Hunan Province education department (14C0911), and the National Institutes of Health and Department of Veterans Administration of USA.

Abbreviations

ACTH	adrenocorticotrophic hormone
AIF	apoptosis inducing factor
AKI	Acute kidney injury
BMSC	bone marrow derived stem cells
CIN	contrast-induced nephropathy
COMP-Ang1	Cartilage oligomeric matrix protein-angiopoietin-1
CysLT1R	cysteinyl leukotriene-1 receptor
DMARD	disease-modifying antirheumatic drugs
eNOS	endothelial nitric oxide synthase
eEPCs	endothelial progenitor cells
HDAC	histone deacetylase
HSPC	hematopoietic stem and progenitor cells
IRI	ischemia-reperfusion injury
ICAM-1	intercellular adhesion molecule-1
JNK	c-Jun N-terminal kinase
KIF3B	kinesin family member 3B
KIM-1	kidney injury molecule 1
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemotactic protein-1
α-MSH	alpha-melanocyte-stimulating hormone
MFG-E8	Milk fat globule-epidermal growth factor-factor VIII
MPT	Mitochondrial permeability transition

MSCs	mesenchymal stem cells
NGAL	neutrophil gelatinase-associated lipocalin
MDM2	murine double minute-2
MMP-2	matrix metalloproteinase 2
mTOR	mammalian target of rapamycin
PI3K	phosphatidylinositol-3 kinase
PACAP	pituitary adenylate cyclase activating polypeptide
RAAS	renin-angiotensin-aldosterone system
RANTES	regulated upon activation normal T-cell expressed and secreted
RIP1	receptor-interacting protein 1
TNF-α	Tumor necrosis factor-alpha
TWEAK	TNF-like weak inducer of apoptosis
VDRA	vitamin D receptor agonist

References

- Agarwal A, Balla J, Alam J, Croatt AJ, Nath KA. Induction of heme oxygenase in toxic renal injury a protective role in cisplatin nephrotoxicity in the rat. *Kidney Int.* 1995; 48(4):1298–1307. [PubMed: 8569092]
- Aguado-Fraile E, Ramos E, Saenz-Morales D, Conde E, Blanco-Sanchez I, Stamatakis K, del Peso L, Cuppen E, Brune B, Garcia Bermejo ML. miR-127 Protects Proximal Tubule Cells against Ischemia/Reperfusion Identification of Kinesin Family Member 3B as miR-127 Target. *PLOS ONE.* 2012; 7:e44305. [PubMed: 22962609]
- An S, Zang X, Yuan W, Zhuge Y, Yu Q. Neutrophil gelatinase-associated lipocalin (NGAL) may play a protective role against rats ischemia/reperfusion renal injury via inhibiting tubular epithelial cell apoptosis. *Ren Fail.* 2013; 35(1):143–149. [PubMed: 23151253]
- Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997; 275(5302):964–967. [PubMed: 9020076]
- Attia DM, Goldschmeding R, Attia MA, Boer P, Koomans HA, Joles JA. Male gender increases sensitivity to renal injury in response to cholesterol loading. *Am J Physiol Renal Physiol.* 2003; 284(4):F718–F726. [PubMed: 12488246]
- Badal SS, Danesh FR. MicroRNAs and their applications in kidney diseases. *Pediatr Nephrol.* 2015; 30(5):727–740. [PubMed: 24928414]
- Baur JA, Sinclair DA. Therapeutic potential of resveratrol the in vivo evidence. *Nat Rev Drug Discov.* 2006; 5(6):493–506. [PubMed: 16732220]
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet.* 2012; 380(9843):756–766. [PubMed: 22617274]
- Bhatt K, Wei Q, Pabla N, Dong G, Mi QS, Liang M, Mei C, Dong Z. MicroRNA-687 Induced by Hypoxia-Inducible Factor-1 Targets Phosphatase and Tensin Homolog in Renal Ischemia-Reperfusion Injury. *J Am Soc Nephrol.* 2015; 26(7):1588–1596. [PubMed: 25587068]

- Bhatt K, Zhou L, Mi QS, Huang S, She JX, Dong Z. MicroRNA-34a is induced via p53 during cisplatin nephrotoxicity and contributes to cell survival. *Mol Med*. 2010; 16(9–10):409–416. [PubMed: 20386864]
- Bijkerk R, van Solingen C, de Boer HC, van der Pol P, Khairoun M, de Bruin RG, van Oeveren-Rietdijk AM, Liewers E, et al. Hematopoietic microRNA-126 protects against renal ischemia/reperfusion injury by promoting vascular integrity. *J Am Soc Nephrol*. 2014; 25(8):1710–1722. [PubMed: 24610930]
- Billings FT 4th, Pretorius M, Siew ED, Yu C, Brown NJ. Early postoperative statin therapy is associated with a lower incidence of acute kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2010; 24(6):913–920. [PubMed: 20599398]
- Birk AV, Liu S, Soong Y, Mills W, Singh P, Warren JD, Seshan SV, Pardee JD, Szeto HH. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. *J Am Soc Nephrol*. 2013; 24(8):1250–1261. [PubMed: 23813215]
- Bitzer M, Ben-Dov IZ, Thum T. Microparticles and microRNAs of endothelial progenitor cells ameliorate acute kidney injury. *Kidney Int*. 2012; 82(4):375–377. [PubMed: 22846811]
- Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest*. 2011; 121(11):4210–4221. [PubMed: 22045571]
- Briguori C, Quintavalle C, De Micco F, Condorelli G. Nephrotoxicity of contrast media and protective effects of acetylcysteine. *Arch Toxicol*. 2011; 85(3):165–173. [PubMed: 21140133]
- Brooks C, Cho SG, Wang CY, Yang T, Dong Z. Fragmented mitochondria are sensitized to Bax insertion and activation during apoptosis. *Am J Physiol Cell Physiol*. 2011; 300(3):C447–C455. [PubMed: 21160028]
- Brooks C, Dong Z. Regulation of mitochondrial morphological dynamics during apoptosis by Bcl-2 family proteins a key in Bak? *Cell Cycle*. 2007; 6(24):3043–3047. [PubMed: 18073534]
- Brooks C, Wei Q, Cho SG, Dong Z. Regulation of mitochondrial dynamics in acute kidney injury in cell culture and rodent models. *J Clin Invest*. 2009; 119(5):1275–1285. [PubMed: 19349686]
- Bruno S, Grange C, Collino F, Derigibus MC, Cantaluppi V, Biancone L, Tetta C, Camussi G. Microvesicles derived from mesenchymal stem cells enhance survival in a lethal model of acute kidney injury. *PLoS One*. 2012; 7(3):e33115. [PubMed: 22431999]
- Canale D, de Braganca AC, Goncalves J, Shimizu MHM, Volpini RA, Andrade L, Seguro AC. Vitamin D deficiency aggravates tenofovir induced metabolic syndrome and renal failure. *Nephrol Dial Transplant*. 2013; 28:115.
- Cao CC, Ding XQ, Ou ZL, Liu CF, Li P, Wang L, Zhu CF. In vivo transfection of NF-kappaB decoy oligodeoxynucleotides attenuate renal ischemia/reperfusion injury in rats. *Kidney Int*. 2004; 65(3):834–845. [PubMed: 14871403]
- Chander V, Chopra K. Protective effect of nitric oxide pathway in resveratrol renal ischemia-reperfusion injury in rats. *Arch Med Res*. 2006; 37(1):19–26. [PubMed: 16314181]
- Chander V, Chopra K. Protective effect of resveratrol, a polyphenolic phytoalexin on glycerol-induced acute renal failure in rat kidney. *Ren Fail*. 2006; 28(2):161–169. [PubMed: 16538975]
- Charles CJ, Lainchbury JG, Nicholls MG, Rademaker MT, Richards AM, Troughton RW. Adrenomedullin and the renin-angiotensin-aldosterone system. *Regul Pept*. 2003; 112(1–3):41–49. [PubMed: 12667624]
- Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014; 371(1):58–66. [PubMed: 24988558]
- Chen J, Chen JK, Harris RC. Deletion of the epidermal growth factor receptor in renal proximal tubule epithelial cells delays recovery from acute kidney injury. *Kidney Int*. 2012; 82(1):45–52. [PubMed: 22418982]
- Chen X, Chen Z, Wang H, Xiong X, Liu X, Hu C, Han Y, Lu Y, Wu Z, Zhang Q. Plasmid pUDK-HGF encoding human hepatocyte growth factor gene attenuates gentamicin-induced kidney injury in rats. *Exp Toxicol Pathol*. 2013; 65(5):541–547. [PubMed: 22551933]
- Chen Y, Qian H, Zhu W, Zhang X, Yan Y, Ye S, Peng X, Li W, Xu W. Hepatocyte growth factor modification promotes the amelioration effects of human umbilical cord mesenchymal stem cells on rat acute kidney injury. *Stem Cells Dev*. 2011; 20(1):103–113. [PubMed: 20446811]

- Chiao H, Kohda Y, McLeroy P, Craig L, Housini I, Star RA. Alpha-melanocyte-stimulating hormone (α -MSH) protects against renal injury after ischemia in mice and rats. *J Clin Invest*. 1997; 99(6): 1165–1172. [PubMed: 9077523]
- Chiao H, Kohda Y, McLeroy P, Craig L, Housini I, Star RA. Alpha-melanocyte-stimulating hormone inhibits renal injury in the absence of neutrophils. *Kidney Int*. 1998; 54(3):765–774. [PubMed: 9734601]
- Choi DE, Jeong JY, Lim BJ, Na KR, Shin YT, Lee KW. Pretreatment with the tumor necrosis factor- α blocker etanercept attenuated ischemia-reperfusion renal injury. *Transplant Proc*. 2009; 41(9):3590–3596. [PubMed: 19917350]
- Choi HM, Jo SK, Kim SH, Lee JW, Cho E, Hyun YY, Cha JJ, Kang YS, Cha DR, Cho WY, Kim HK. Glucocorticoids attenuate septic acute kidney injury. *Biochem Biophys Res Commun*. 2013; 435(4):678–684. [PubMed: 23702481]
- Chung AC, Lan HY. MicroRNAs in renal fibrosis. *Front Physiol*. 2015; 6:50. [PubMed: 25750628]
- Cianciolo, Cosentino C.; Skrypnik, NI.; Brilli, LL.; Chiba, T.; Novitskaya, T.; Woods, C.; West, J.; Korotchenko, VN.; McDermott, L.; Day, BW.; Davidson, AJ.; Harris, RC.; de Caestecker, MP.; Hukriede, NA. Histone deacetylase inhibitor enhances recovery after AKI. *J Am Soc Nephrol*. 2013; 24(6):943–953. [PubMed: 23620402]
- Conde E, Alegre L, Blanco-Sánchez I, Sáenz-Morales D, Aguado-Fraile E, Ponte B, et al. Hypoxia inducible factor 1- α (HIF-1 α) is induced during reperfusion after renal ischemia and is critical for proximal tubule cell survival. *PLoS One*. 2012; 7(3):e33258. [PubMed: 22432008]
- Dashti-Khavidaki S, Moghaddas A, Heydari B, Khalili H, Lessan-Pezeshki M, Lessan-Pezeshki M. Statins against drug-induced nephrotoxicity. *J Pharm Pharm Sci*. 2013; 16(4):588–608. [PubMed: 24210066]
- Datta K, Suman S, Fornace AJ Jr. Radiation persistently promoted oxidative stress, activated mTOR via PI3K/Akt, and downregulated autophagy pathway in mouse intestine. *Int J Biochem Cell Biol*. 2014; 57:167–176. [PubMed: 25449263]
- Demirebilek S, Karaman A, Baykarabulut A, Akin M, Gürünlüoğlu K, Edali MN, et al. Polyenylphosphatidylcholine pretreatment ameliorates ischemic acute renal injury in rats. *Int J Urol*. 2006; 13(6):747–753. [PubMed: 16834655]
- Deng J, Kohda Y, Chiao H, Wang Y, Hu X, Hewitt SM, Miyaji T, McLeroy P, Nibhanupudiy B, Li S, Star RA. Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. *Kidney Int*. 2001; 60(6):2118–2128. [PubMed: 11737586]
- Doi K, Hu X, Yuen PS, Leelahavanichkul A, Yasuda H, Kim SM, Schnermann J, Jonassen TE, Frøkiaer J, Nielsen S, Star RA. AP214, an analogue of alpha-melanocyte-stimulating hormone, ameliorates sepsis-induced acute kidney injury and mortality. *Kidney Int*. 2008; 73(11):1266–1274. [PubMed: 18354376]
- Dong G, Liu Y, Zhang L, Huang S, Ding HF, Dong Z. mTOR contributes to ER stress and associated apoptosis in renal tubular cells. *Am J Physiol Renal Physiol*. 2015; 308(3):F267–F274. [PubMed: 25428129]
- Dong G, Luo J, Kumar V, Dong Z. Inhibitors of histone deacetylases suppress cisplatin-induced p53 activation and apoptosis in renal tubular cells. *Am J Physiol Renal Physiol*. 2010; 298(2):F293–F300. [PubMed: 19889954]
- Dong G, Wang L, Wang CY, Yang T, Kumar MV, Dong Z. Induction of apoptosis in renal tubular cells by histone deacetylase inhibitors, a family of anticancer agents. *J Pharmacol Exp Ther*. 2008; 325(3):978–984. [PubMed: 18310471]
- Du T, Cheng J, Zhong L, Zhao XF, Zhu J, Zhu YJ, Liu GH. The alleviation of acute and chronic kidney injury by human Wharton's jelly-derived mesenchymal stromal cells triggered by ischemia-reperfusion injury via an endocrine mechanism. *Cytotherapy*. 2012; 14(10):1215–1227. [PubMed: 22920838]
- Duffield JS, Park KM, Hsiao LL, Kelley VR, Scadden DT, Ichimura T, Bonventre JV. Restoration of tubular epithelial cells during repair of the postischemic kidney occurs independently of bone marrow-derived stem cells. *J Clin Invest*. 2005; 115(7):1743–1755. [PubMed: 16007251]

- Duru M, Nacar A, Yönden Z, Kuvandik G, Helvacı MR, Sö üt S, et al. Protective effects of N-acetylcysteine on cyclosporine-A-induced nephrotoxicity. *Ren Fail.* 2008; 30(4):453–459. [PubMed: 18569921]
- Fähling M, Mathia S, Paliege A, Koesters R, Mrowka R, Peters H, Persson PB, Neumayer HH, Bachmann S, Rosenberger C. Tubular von Hippel-Lindau knockout protects against rhabdomyolysis-induced AKI. *J Am Soc Nephrol.* 2013; 24(11):1806–1819. [PubMed: 23970125]
- Faubel S, Chawla LS, Chertow GM, Goldstein SL, Jaber BL, Liu KD. Acute Kidney Injury Advisory Group of the American Society of Nephrology. Ongoing clinical trials in AKI. *Clin J Am Soc Nephrol.* 2012; 7(5):861–873. [PubMed: 22442183]
- Feldkamp T, Park JS, Pasupulati R, Amora D, Roeser NF, Venkatachalam MA, Weinberg JM. Regulation of the mitochondrial permeability transition in kidney proximal tubules and its alteration during hypoxia-reoxygenation. *Am J Physiol Renal Physiol.* 2009; 297:F1632–F1646. [PubMed: 19741014]
- Fernández M, Medina A, Santos F, Carbajo E, Rodríguez J, Alvarez J, Cobo A. Exacerbated inflammatory response induced by insulin-like growth factor I treatment in rats with ischemic acute renal failure. *J Am Soc Nephrol.* 2001; 12(9):1900–1907. [PubMed: 11518783]
- Fleig SV, Humphreys BD. Rationale of mesenchymal stem cell therapy in kidney injury. *Nephron Clin Pract.* 2014; 127(1–4):75–80. [PubMed: 25343826]
- Fouad AA, Qureshi HA, Al-Sultan AI, Yacoubi MT, Al-Melhim WN. Nephroprotective effect of telmisartan in rats with ischemia/reperfusion renal injury. *Pharmacology.* 2010; 85(3):158–167. [PubMed: 20150754]
- Friedlaender M, Popovtzer MM, Weiss O, Nefesh I, Kopolovic J, Raz I. Insulin-like growth factor-1 (IGF-1) enhances recovery from HgCl₂-induced acute renal failure the effects on renal IGF-1, IGF-1 receptor, and IGF-binding protein-1 mRNA. *J Am Soc Nephrol.* 1995; 5(10):1782–1791. [PubMed: 7540432]
- Fuller TF, Kusch A, Chaykovska L, Catar R, Pützer J, Hoff U, Dragun D, et al. Protein kinase C inhibition ameliorates posttransplantation preservation injury in rat renal transplants. *Transplantation.* 2012; 94(7):679–686. [PubMed: 22932117]
- Funk JA, Schnellmann RG. Persistent disruption of mitochondrial homeostasis after acute kidney injury. *Am J Physiol Renal Physiol.* 2012; 302(7):F853–F864. [PubMed: 22160772]
- Funk JA, Schnellmann RG. Accelerated recovery of renal mitochondrial and tubule homeostasis with SIRT1/PGC-1 α activation following ischemia-reperfusion injury. *Toxicol Appl Pharmacol.* 2013; 273(2):345–354. [PubMed: 24096033]
- Gandolfo MT, Jang HR, Bagnasco SM, Ko GJ, Agreda P, Satpute SR, Crow MT, King LS, Rabb H. Foxp3+ regulatory T cells participate in repair of ischemic acute kidney injury. *Kidney Int.* 2009; 76(7):717–729. [PubMed: 19625990]
- Gao G, Zhang B, Ramesh G, Betterly D, Tadagavadi RK, Wang W, Reeves WB. TNF- α mediates increased susceptibility to ischemic AKI in diabetes. *Am J Physiol Renal Physiol.* 2013; 304(5):F515–F521. [PubMed: 23283990]
- Gatti S, Bruno S, Deregis MC, Sordi A, Cantaluppi V, Tetta C, Camussi G. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. *Nephrol Dial Transplant.* 2011; 26(5):1474–1483. [PubMed: 21324974]
- Godwin JG, Ge X, Stephan K, Jurisch A, Tullius SG, Iacomini J. Identification of a microRNA signature of renal ischemia reperfusion injury. *Proc Natl Acad Sci U S A.* 2010; 107(32):14339–14344. [PubMed: 20651252]
- Golestaneh L, Lindsey K, Malhotra P, Kargoli F, Friedman A, El-Achkar TM, et al. Acute kidney injury after cardiac surgery is minocycline protective? *J Nephrol.* 2015; 28(2):193–199. [PubMed: 25348221]
- Gueler F, Rong S, Park JK, Fiebeler A, Menne J, Kunter U, et al. Postischemic acute renal failure is reduced by short-term statin treatment in a rat model. *J Am Soc Nephrol.* 2002; 13(9):2288–2298. [PubMed: 12191973]
- Gui D, Huang J, Liu W, Guo Y, Xiao W, Wang N. Astragaloside IV prevents acute kidney injury in two rodent models by inhibiting oxidative stress and apoptosis pathways. *Apoptosis.* 2013; 18(4):409–422. [PubMed: 23325448]

- Haase VH. Mechanisms of hypoxia responses in renal tissue. *J Am Soc Nephrol.* 2013; 24(4):537–541. [PubMed: 23334390]
- Hanan, H Hagar; Raeesa, Abd El Tawab. Cysteinyl leukotriene receptor antagonism alleviates renal injury induced by ischemia-reperfusion in rats. *J Surg Res.* 2012; 178(1):e25–e34. [PubMed: 22487384]
- He B, Ying-Tian Z, Xin-Gang Y, Jing-Song S, Guang-Hui W, Tao L. Protective effects of Radix Codonopsis on ischemia–reperfusion injury in rats after kidney transplantation. *Pediatr Surg Int.* 2011; 27(11):1203–1212. [PubMed: 21691763]
- He S, Liu N, Bayliss G, Zhuang S. EGFR activity is required for renal tubular cell dedifferentiation and proliferation in a murine model of folic acid-induced acute kidney injury. *Am J Physiol Renal Physiol.* 2013; 304(4):F356–F366. [PubMed: 23255615]
- Hill P, Shukla D, Tran MG, Aragonés J, Cook HT, Carmeliet P, Maxwell PH. Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol.* 2008; 19(1):39–46. [PubMed: 18178798]
- Holthoff JH, Wang Z, Seely KA, Gokden N, Mayeux PR. Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury. *Kidney Int.* 2012; 81(4):370–378. [PubMed: 21975863]
- Homsí E, Janino P, Amano M, Saraiva Camara NO. Endogenous hepatocyte growth factor attenuates inflammatory response in glycerol-induced acute kidney injury. *Am J Nephrol.* 2009; 29(4):283–291. [PubMed: 18824844]
- Horvath G, Racz B, Reglodi D, Kovacs K, Kiss P, Gallyas F Jr, Bogner Z, Szabo A, et al. Effects of PACAP on mitochondrial apoptotic pathways and cytokine expression in rats subjected to renal ischemia/reperfusion. *J Mol Neurosci.* 2010; 42(3):411–418. [PubMed: 20229361]
- Howell GM, Gomez H, Collage RD, Loughran P, Zhang X, Matthew R Rosengart, et al. Augmenting Autophagy to Treat Acute Kidney Injury during Endotoxemia in Mice. *PLoS ONE.* 2013; 8:e69520. [PubMed: 23936035]
- Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Sinclair DA, et al. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature.* 2003; 425(6954):191–196. [PubMed: 12939617]
- Hsu CY, McCulloch CE, Fan D, Ordoñez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. *Kidney Int.* 2007; 72(2):208–212. [PubMed: 17507907]
- Hsu DZ, Li YH, Chu PY, Periasamy S, Liu MY. Sesame oil prevents acute kidney injury induced by the synergistic action of aminoglycoside and iodinated contrast in rats. *Antimicrob Agents Chemother.* 2011; 55(6):2532–2536. [PubMed: 21402854]
- Hsu DZ, Liu CT, Li YH, Chu PY, Liu MY. Protective effect of daily sesame oil supplement on gentamicin-induced renal injury in rats. *Shock.* 2010; 33(1):88–92. [PubMed: 19487986]
- Hu J, Zhang L, Wang N, Ding R, Cui S, Zhu F, Xie Y, Sun X, Wu D, Hong Q, Li Q, Shi S, Liu X, Chen X. Mesenchymal stem cells attenuate ischemic acute kidney injury by inducing regulatory T cells through splenocyte interactions. *Kidney Int.* 2013; 84(3):521–531. [PubMed: 23615497]
- Huang L, Belousova T, Chen M, DiMattia G, Liu D, Sheikh-Hamad D. Overexpression of stanniocalcin-1 inhibits reactive oxygen species and renal ischemia/reperfusion injury in mice. *Kidney Int.* 2012; 82(8):867–877. [PubMed: 22695329]
- Hull TD, Kamal AI, Boddu R, Bolisetty S, Guo L, Agarwal A, et al. Heme Oxygenase-1 Regulates Myeloid Cell Trafficking in AKI. *J Am Soc Nephrol.* 2015; 26(9):2139–2151. [PubMed: 25677389]
- Hutchens MP, Fujiyoshi T, Komers R, Herson PS, Anderson S. Estrogen protects renal endothelial barrier function from ischemia-reperfusion in vitro and in vivo. *Am J Physiol Renal Physiol.* 2012; 303(3):F377–F385. [PubMed: 22622457]
- Hutchens MP, Nakano T, Kosaka Y, Dunlap J, Zhang W, Herson PS, Murphy SJ, Anderson S, Hurn PD. Estrogen is renoprotective via a nonreceptor-dependent mechanism after cardiac arrest in vivo. *Anesthesiology.* 2010; 112(2):395–405. [PubMed: 20068453]
- Hwang HS, Choi YA, Park KC, Yang KJ, Choi HS, Kim SH, et al. Pretreatment with rituximab prevents subsequent ischemia-reperfusion injury in mice kidney. *Nephrology Dialysis Transplantation.* 2013; 28:96.

- Hwang HS, Yang KJ, Park KC, Choi HS, Kim SH, Yang CW, et al. Pretreatment with paricalcitol attenuates inflammation in ischemia-reperfusion injury via the up-regulation of cyclooxygenase-2 and prostaglandin E2. *Nephrol Dial Transplant*. 2013; 28(5):1156–1166. [PubMed: 23229926]
- Ihtiyar E, Ya ar NF, Erkasap N, Köken T, Tosun M, Oner S, Erkasap S. Effects of doxycycline on renal ischemia reperfusion injury induced by abdominal compartment syndrome. *J Surg Res*. 2011; 167(1):113–120. [PubMed: 20080260]
- Imberti B, Morigi M, Tomasoni S, Rota C, Corna D, Longaretti L, Rottoli D, Valsecchi F, Benigni A, Wang J, Abbate M, Zoja C, Remuzzi G. Insulin-like growth factor-1 sustains stem cell mediated renal repair. *J Am Soc Nephrol*. 2007; 18:2921–2928. [PubMed: 17942965]
- Inal S, Koc E, Okyay GU, Pasaoglu O, Gonul I, Oyar E, Pasaoglu H, Guz G. Protective effect of adrenomedullin on contrast induced nephropathy in rats. *Nephrology Dialysis Transplantation*. 2013; 28(1 suppl):110.
- Jang HJ, Jeong EK, Kim SS, Lee JH, Oh MY, Kang KS, et al. Protective effect of artemisia asiatica extract against renal ischemia-reperfusion injury in mice. *Exp Clin Transplant*. 2015; 13(1 Suppl): 377–382.
- Jang HR, Rabb H. Immune cells in experimental acute kidney injury. *Nat Rev Nephrol*. 2015; 11(2): 88–101. [PubMed: 25331787]
- Jesinkey SR, Funk JA, Stallons LJ, Wills LP, Megyesi JK, Beeson CC, Schnellmann RG. Formoterol restores mitochondrial and renal function after ischemia-reperfusion injury. *J Am Soc Nephrol*. 2014; 25(6):1157–1162. [PubMed: 24511124]
- Jiang M, Pabla N, Murphy RF, Yang T, Yin XM, Degenhardt K, White E, Dong Z. Nutlin-3 Protects Kidney Cells during Cisplatin Therapy by Suppressing Bax/Bak Activation. *J Biol Chem*. 282(4): 2636–2645.
- Jiang M, Wei Q, Dong G, Komatsu M, Su Y, Dong Z. Autophagy in proximal tubules protects against acute kidney injury. *Kidney Int*. 2012; 82(12):1271–1283. [PubMed: 22854643]
- Jiang T, Tian F, Zheng H, Whitman SA, Lin Y, Zhang Z, Zhang N, Zhang DD. Nrf2 suppresses lupus nephritis through inhibition of oxidative injury and the NF- κ B-mediated inflammatory response. *Kidney Int*. 2014; 85(2):333–343. [PubMed: 24025640]
- Jo SK, Rosner MH, Okusa MD. Pharmacologic treatment of acute kidney injury why drugs haven't worked and what is on the horizon. *Clin J Am Soc Nephrol*. 2007; 2(2):356–365. [PubMed: 17699435]
- Jones EA, Shoskes DA. The effect of mycophenolate mofetil and polyphenolic bioflavonoids on renal ischemia reperfusion injury and repair. *J Urol*. 2000; 163(3):999–1004. [PubMed: 10688038]
- Jung CH, Ro SH, Cao J, Otto NM, Kim DH. mTOR regulation of autophagy. *FEBS Lett*. 2010; 584(7): 1287–1295. [PubMed: 20083114]
- Jung HS, Joo JD, Kim DW, In JH, Roh M, Jeong JT, Noh SJ, Choi JW. Effect of milrinone on the inflammatory response and NF- κ B activation in renal ischemia-reperfusion injury in mice. *Korean J Anesthesiol*. 2014; 66(2):136–142. [PubMed: 24624272]
- Jung YJ, Kim DH, Lee AS, Lee S, Kang KP, Lee SY, Jang KY, Sung MJ, Park SK, Kim W. Peritubular capillary preservation with COMP-angiopoietin-1 decreases ischemia-reperfusion-induced acute kidney injury. *Am J Physiol Renal Physiol*. 2009; 297(4):F952–F960. [PubMed: 19656917]
- Jung YJ, Lee JE, Lee AS, Kang KP, Lee S, Park SK, Lee SY, Han MK, Kim DH, Kim W. SIRT1 overexpression decreases cisplatin-induced acetylation of NF- κ B p65 subunit and cytotoxicity in renal proximal tubule cells. *Biochem Biophys Res Commun*. 2012; 419(2):206–210. [PubMed: 22330808]
- Kahraman A, Erkasap N, Serteser M, Köken T. Protective effect of quercetin on renal ischemia/reperfusion injury in rats. *J Nephrol*. 2003; 16(2):219–224. [PubMed: 12768068]
- Kale S, Karihaloo A, Clark PR, Kashgarian M, Krause DS, Cantley LG. Bone marrow stem cells contribute to repair of the ischemically injured renal tubule. *J Clin Invest*. 2003; 112(1):42–49. [PubMed: 12824456]
- Kapitsinou PP, Jaffe J, Michael M, Swan CE, Duffy KJ, Erickson-Miller CL, Haase VH. Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. *Am J Physiol Renal Physiol*. 2012; 302(9):F1172–F1179. [PubMed: 22262480]

- Kapitsinou PP, Sano H, Michael M, Kobayashi H, Davidoff O, Bian A, Yao B, Zhang MZ, Harris RC, Duffy KJ, Erickson-Miller CL, Sutton TA, Haase VH. Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury. *J Clin Invest*. 2014; 124(6):2396–2409. [PubMed: 24789906]
- Karaman A, Turkmen E, Gursul C, Tas E, Fadillioglu E. Prevention of renal ischemia/reperfusion-induced injury in rats by leflunomide. *Int J Urol*. 2006; 13(11):1434–1441. [PubMed: 17083399]
- Katsuno T, Ozaki T, Saka Y, Furuhashi K, Kim H, Yasuda K, Yamamoto T, Sato W, Tsuboi N, Mizuno M, Ito Y, Imai E, Matsuo S, Maruyama S. Low serum cultured adipose tissue-derived stromal cells ameliorate acute kidney injury in rats. *Cell Transplant*. 2013; 22(2):287–297. [PubMed: 22963874]
- Kazunori, Takahashi; Hiroki, Mizukami; Kosuke, Kamata; Wataru, Inaba; Noriaki, Kato; Chihiro, Hibi; Soroku, Yagihashi. Amelioration of Acute Kidney Injury in Lipopolysaccharide-Induced Systemic Inflammatory Response Syndrome by an Aldose Reductase Inhibitor, Fidarestat. *PLoS One*. 2012; 7:e30134. [PubMed: 22253906]
- Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med*. 2008; 148(4):284–294. [PubMed: 18283206]
- Kelly KJ, Burford JL, Dominguez JH. Postischemic inflammatory syndrome a critical mechanism of progression in diabetic nephropathy. *Am J Physiol Renal Physiol*. 2009; 297(4):F923–F931. [PubMed: 19656916]
- Kelly KJ, Sutton TA, Weathered N, Ray N, Caldwell EJ, Plotkin Z, Dagher PC. Minocycline inhibits apoptosis and inflammation in a rat model of ischemic renal injury. *Am J Physiol Renal Physiol*. 2004; 287(4):F760–F766. [PubMed: 15172883]
- Kelly KJ, Williams WW Jr, Colvin RB, Meehan SM, Springer TA, Gutierrez-Ramos JC, Bonventre JV. Interleukin-1-deficient mice are protected against ischemic renal injury. *J Clin Invest*. 1996; 97(4):1056–1063. [PubMed: 8613529]
- Kelly KJ, Williams WW Jr, Colvin RB, Bonventre JV. Antibody to interleukin-1 protects the kidney against ischemic injury. *Proc Natl Acad Sci U S A*. 1994; 91(2):812–816. [PubMed: 7904759]
- Khan NA, Susa D, van Den Berg JW, Huisman M, Ameling MH, van den Engel S, Roest HP, Ijzermans JN, Dik WA, Benner R, de Bruin RW. Amelioration of renal ischaemia-reperfusion injury by synthetic oligopeptides related to human chorionic gonadotropin. *Nephrol Dial Transplant*. 2009; 24(9):2701–2708. [PubMed: 19633318]
- Kholmukhamedov A, Czerny C, Hu J, Schwartz J, Zhong Z, Lemasters JJ. Minocycline and doxycycline, but not tetracycline, mitigate liver and kidney injury after hemorrhagic shock/resuscitation. *Shock*. 2014; 42(3):256–263. [PubMed: 24978888]
- Kidney Disease, Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Kidney Int*. 2012; (2 Suppl):1–138.
- Kim DH, Jung YJ, Lee JE, Lee AS, Kang KP, Kim W, et al. SIRT1 activation by resveratrol ameliorates cisplatin-induced renal injury through deacetylation of p53. *Am J Physiol Renal Physiol*. 2011; 301(2):F427–F435. [PubMed: 21593185]
- Kim JI, Jung KJ, Jang HS, Park KM. Gender-specific role of HDAC11 in kidney ischemia- and reperfusion-induced PAI-1 expression and injury. *Am J Physiol Renal Physiol*. 2013; 305(1):F61–F70. [PubMed: 23657855]
- Kim W, Moon SO, Lee SY, Jang KY, Cho CH, Koh GY, Choi KS, Yoon KH, Sung MJ, Kim DH, Lee S, Kang KP, Park SK. COMP-angiopoietin-1 ameliorates renal fibrosis in a unilateral ureteral obstruction model. *J Am Soc Nephrol*. 2006; 17(9):2474–2483. [PubMed: 16885409]
- Kim YJ, Lee MY, Son HY, Park BK, Ryu SY, Jung JY. Red ginseng ameliorates acute cisplatin-induced nephropathy. *Planta Med*. 2014; 80(8–9):645–654. [PubMed: 24963615]
- Kim YS, Jung MH, Choi MY, Kim YH, Sheverdin V, Kim JH, Ha HJ, Park DJ, et al. Glutamine attenuates tubular cell apoptosis in acute kidney injury via inhibition of the c-Jun N-terminal kinase phosphorylation of 14-3-3. *Crit Care Med*. 2009; 37(6):2033–2044. [PubMed: 19384198]

- Kinsey GR, Sharma R, Huang L, Li L, Vergis AL, Ye H, Ju ST, Okusa MD. Regulatory T cells suppress innate immunity in kidney ischemia-reperfusion injury. *J Am Soc Nephrol*. 2009; 20(8):1744–1753. [PubMed: 19497969]
- Kostapanos MS, Liberopoulos EN, Elisaf MS. Statin pleiotropy against renal injury. *J Cardiometa Syndr*. 2009; 4(1):E4–E9. [PubMed: 19245508]
- Lai LW, Yong KC, Lien YH. Pharmacologic recruitment of regulatory T cells as a therapy for ischemic acute kidney injury. *Kidney Int*. 2012; 81(10):983–992. [PubMed: 22189844]
- Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury an increasing global concern. *Lancet*. 2013; 382(9887):170–179. [PubMed: 23727171]
- Lauver DA, Carey EG, Bergin IL, Lucchesi BR, Gurm HS. Sildenafil citrate for prophylaxis of nephropathy in an animal model of contrast-induced acute kidney injury. *PLoS One*. 2014; 9(11):e113598. [PubMed: 25426714]
- Lee YK, Chin YW, Choi YH. Effects of Korean red ginseng extract on acute renal failure induced by gentamicin and pharmacokinetic changes by metformin in rats. *Food Chem Toxicol*. 2013; 59:153–159. [PubMed: 23743120]
- Levine MH, Wang Z, Bhatti TR, Wang Y, Aufhauser DD, McNeal S, Liu Y, Cheraghlou S, Han R, Wang L, Hancock WW. Class-specific histone/protein deacetylase inhibition protects against renal ischemia reperfusion injury and fibrosis formation. *Am J Transplant*. 2015; 15(4):965–973. [PubMed: 25708614]
- Li L, Black R, Ma Z, Yang Q, Wang A, Lin F. Use of mouse hematopoietic stem and progenitor cells to treat acute kidney injury. *Am J Physiol Renal Physiol*. 2012; 302(1):F9–F19. [PubMed: 21937606]
- Li L, Truong P, Igarashi P, Lin F. Renal and bone marrow cells fuse after renal ischemic injury. *J Am Soc Nephrol*. 2007; 18(12):3067–3077. [PubMed: 18003777]
- Li Y, Xia AZ, Xing SH. Protective effect of edaravone against renal ischemia/reperfusion injury and compared with ischemic postconditioning in rats. *Yao Xue Xue Bao*. 2010; 45(7):840–848. [PubMed: 20931780]
- Liaño F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. *Kidney Int*. 1998; (66 Suppl):S16–S24.
- Lieberthal W, Levine JS. Mammalian target of rapamycin and the kidney. I. The signaling pathway. *Am J Physiol Renal Physiol*. 2012; 303(1):F1–F10. [PubMed: 22419691]
- Linkermann A, Bräsen JH, Himmerkus N, Liu S, Huber TB, Kunzendorf U, Krautwald S. Rip1 (receptor-interacting protein kinase 1) mediates necroptosis and contributes to renal ischemia/reperfusion injury. *Kidney Int*. 2012; 81(8):751–761. [PubMed: 22237751]
- Linkermann A, Chen G, Dong G, Kunzendorf U, Krautwald S, Dong Z. Regulated cell death in AKI. *J Am Soc Nephrol*. 2014; 25(12):2689–2701. [PubMed: 24925726]
- Linkermann A, Heller JO, Prókai A, Weinberg JM, De Zen F, Krautwald S, et al. The RIP1-kinase inhibitor necrostatin-1 prevents osmotic nephrosis and contrast-induced AKI in mice. *J Am Soc Nephrol*. 2013; 24(10):1545–1557. [PubMed: 23833261]
- Liu N, Patzak A, Zhang J. CXCR4-overexpressing bone marrow-derived mesenchymal stem cells improve repair of acute kidney injury. *Am J Physiol Renal Physiol*. 2013; 305(7):F1064–F1073. [PubMed: 23884141]
- Liu N, Tolbert E, Pang M, Ponnusamy M, Yan H, Zhuang S. Suramin inhibits renal fibrosis in chronic kidney disease. *J Am Soc Nephrol*. 2011; 22(6):1064–1075. [PubMed: 21617121]
- Liu P, Feng Y, Dong C, Liu D, Wu X, Wu H, Lv P, Zhou Y. Study on therapeutic action of bone marrow derived mesenchymal stem cell combined with vitamin E against acute kidney injury in rats. *Life Sci*. 2013; 92:829–837. [PubMed: 23499556]
- Lorenzen JM, Kaucsar T, Schauerte C, Schmitt R, Rong S, Hübner A, Scherf K, Fiedler J, Martino F, Kumarswamy R, Kölling M, Sörensen I, et al. MicroRNA-24 Antagonism Prevents Renal Ischemia Reperfusion Injury. *J Am Soc Nephrol*. 2014; 25:2717–2729. [PubMed: 24854275]
- Maines MD, Mayer RD, Ewing JF, McCoubrey WK Jr. Induction of kidney heme oxygenase-1 (HSP32) mRNA and protein by ischemia/reperfusion possible role of heme as both promotor of

- tissue damage and regulator of HSP32. *J Pharmacol Exp Ther.* 1993; 264(1):457–462. [PubMed: 8423544]
- Mar D, Gharib SA, Zager RA, Johnson A, Denisenko O, Bomszyk K. Heterogeneity of epigenetic changes at ischemia/reperfusion- and endotoxin-induced acute kidney injury genes. *Kidney Int.* 2015; 88(4):734–744. [PubMed: 26061546]
- Marrone AK, Ho J. MicroRNAs potential regulators of renal development genes that contribute to CAKUT. *Pediatr Nephrol.* 2014; 29(4):565–574. [PubMed: 23996519]
- Martins PS, Kallas EG, Neto MC, Dalboni MA, Blecher S, Salomão R. Upregulation of reactive oxygen species generation and phagocytosis, and increased apoptosis in human neutrophils during severe sepsis and septic shock. *Shock.* 2003; 20(3):208–212. [PubMed: 12923490]
- Mason S, Hader C, Marlier A, Moeckel G, Cantley LG. Met activation is required for early cytoprotection after ischemic kidney injury. *J Am Soc Nephrol.* 2014; 25(2):329–337. [PubMed: 24136921]
- Matsuda A, Wu R, Jacob A, Komura H, Zhou M, Wang Z, Aziz MM, Wang P. Protective effect of milk fat globule-epidermal growth factor-factor VIII after renal ischemia-reperfusion injury in mice. *Crit Care Med.* 2011; 39(9):2039–2047. [PubMed: 21666453]
- Matsui K, Kamijo-Ikemori A, Sugaya T, Yasuda T, Kimura K. Renal liver-type fatty acid binding protein (L-FABP) attenuates acute kidney injury in aristolochic acid nephrotoxicity. *Am J Pathol.* 2011; 178(3):1021–1032. [PubMed: 21356355]
- Matsumoto M, Makino Y, Tanaka T, Tanaka H, Ishizaka N, Noiri E, Fujita T, Nangaku M. Induction of renoprotective gene expression by cobalt ameliorates ischemic injury of the kidney in rats. *J Am Soc Nephrol.* 2003; 14(7):1825–1832. [PubMed: 12819242]
- Mias C, Trouche E, Seguelas MH, Calcagno F, Dignat-George F, Sabatier F, Piercecchi-Marti MD, Daniel L, Bianchi P, Calise D, Bourin P, Parini A, Cussac D. Ex vivo pretreatment with melatonin improves survival, proangiogenic / mitogenic activity, and efficiency of mesenchymal stem cells injected into ischemic kidney. *Stem Cells.* 2008; 26(7):1749–1757. [PubMed: 18467662]
- Miller SB, Martin DR, Kissane J, Hammerman MR. Insulin-like growth factor I accelerates recovery from ischemic acute tubular necrosis in the rat. *Proc Natl Acad Sci U S A.* 1992; 89(24):11876–11880. [PubMed: 1465411]
- Miyaji T, Hu X, Star RA. alpha-Melanocyte-stimulating hormone and interleukin-10 do not protect the kidney against mercuric chloride-induced injury. *Am J Physiol Renal Physiol.* 2002; 282(5):F795–F801. [PubMed: 11934688]
- Molitoris BA. Therapeutic translation in acute kidney injury the epithelial/endothelial axis. *J Clin Invest.* 2014; 124(6):2355–2363. [PubMed: 24892710]
- Molnar A, Coca S, Devereaux P, Jain A, Kitchlu A, Luo J, et al. Statin use is associated with a lower incidence of acute kidney injury after major elective surgery. *J Am Soc Nephrol.* 2011; 22(5):939–946. [PubMed: 21493769]
- Moore E, Bellomo R. Erythropoietin (EPO) in acute kidney injury. *Ann Intensive Care.* 2011; 1(1):3. [PubMed: 21906325]
- Morigi M, Benigni A. Mesenchymal stem cells and kidney repair. *Nephrol Dial Transplant.* 2013; 28(4):788–793. [PubMed: 23258756]
- Nath KA. Heme oxygenase-1 and acute kidney injury. *Curr Opin Nephrol Hypertens.* 2014; 23(1):17–24. [PubMed: 24275768]
- Nath KA, Balla G, Vercellotti GM, Balla J, Jacob HS, Levitt MD, Rosenberg ME. Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest.* 1992; 90(1):267–270. [PubMed: 1634613]
- Oh GS, Kim HJ, Choi JH, Shen A, Choe SK, Karna A, Lee SH, Jo HJ, Yang SH, Kwak TH, Lee CH, Park R, So HS. Pharmacological activation of NQO1 increases NAD⁺ levels and attenuates cisplatin-mediated acute kidney injury in mice. *Kidney Int.* 2014; 85(3):547–560. [PubMed: 24025646]
- Pabla N, Dong G, Jiang M, Huang S, Kumar MV, Messing RO, Dong Z. Inhibition of PKC δ reduces cisplatin-induced nephrotoxicity without blocking chemotherapeutic efficacy in mouse models of cancer. *J Clin Invest.* 2011; 121(7):2709–2722. [PubMed: 21633170]

- Pabla N, Dong G, Jiang M, Huang S, Kumar MV, Messing RO, Dong Z. Inhibition of PKC δ reduces cisplatin-induced nephrotoxicity without blocking chemotherapeutic efficacy in mouse models of cancer. *J Clin Invest*. 2011; 121(7):2709–2722. [PubMed: 21633170]
- Padanilam BJ. Induction and subcellular localization of protein kinase C isozymes following renal ischemia. *Kidney Int*. 2001; 59(5):1789–1797. [PubMed: 11318949]
- Pan JS, Huang L, Belousova T, Lu L, Yang Y, Reddel R, Chang A, Ju H, DiMattia G, Tong Q, Sheikh-Hamad D. Stanniocalcin-1 inhibits renal ischemia/reperfusion injury via an AMP-activated protein kinase-dependent pathway. *J Am Soc Nephrol*. 2015; 26(2):364–378. [PubMed: 25012175]
- Park JS, Pasupulati R, Feldkamp T, Roeser NF, Weinberg JM. Cyclophilin D and the mitochondrial permeability transition in kidney proximal tubules after hypoxic and ischemic injury. *Am J Physiol Renal Physiol*. 2011; 301(1):F134–F150. [PubMed: 21490135]
- Park KM, Kim JI, Ahn Y, Bonventre AJ, Bonventre JV. Testosterone is responsible for enhanced susceptibility of males to ischemic renal injury. *J Biol Chem*. 2004; 279(50):52282–52292. [PubMed: 15358759]
- Patschan D, Hildebrandt A, Rinneburger J, Wessels JT, Patschan S, Becker JU, Henze E, Krüger A, Müller GA. The hormone melatonin stimulates renoprotective effects of "early outgrowth" endothelial progenitor cells in acute ischemic kidney injury. *Am J Physiol Renal Physiol*. 2012; 302(10):F1305–F1312. [PubMed: 22357919]
- Patschan D, Krupinca K, Patschan S, Zhang Z, Hamby C, Goligorsky MS. Dynamics of mobilization and homing of endothelial progenitor cells after acute renal ischemia modulation by ischemic preconditioning. *Am J Physiol Renal Physiol*. 2006; 291(1):F176–F185. [PubMed: 16478972]
- Patschan D, Patschan S, Wessels JT, Becker JU, David S, Henze E, Goligorsky MS, Müller GA. Epac-1 activator 8-O-cAMP augments renoprotective effects of syngeneic [corrected] murine EPCs in acute ischemic kidney injury. *Am J Physiol Renal Physiol*. 2010; 298(1):F78–F85. [PubMed: 19906949]
- Patschan SA, Patschan D, Temme J, Korsten P, Wessels JT, Koziolok M, Henze E, Müller GA. Endothelial progenitor cells (EPC) in sepsis with acute renal dysfunction (ARD). *Crit Care*. 2011; 15(2):R94. [PubMed: 21396100]
- Pellegrini KL, Han T, Bijol V, Saikumar J, Craciun FL, Chen WW, Fuscoe JC, Vaidya VS. MicroRNA-155 deficient mice experience heightened kidney toxicity when dosed with cisplatin. *Toxicol Sci*. 2014; 141(2):484–492. [PubMed: 25015656]
- Peng J, Li X, Zhang D, Chen JK, Su Y, Smith SB, Dong Z. Hyperglycemia, p53, and mitochondrial pathway of apoptosis are involved in the susceptibility of diabetic models to ischemic acute kidney injury. *Kidney Int*. 2015; 87(1):137–150. [PubMed: 24963915]
- Peng ZY, Zhou F, Wang HZ, Wen XY, Nolin TD, Bishop JV, Kellum JA. The anti-oxidant effects are not the main mechanism for glutamine's protective effects on acute kidney injury in mice. *Eur J Pharmacol*. 2013; 705(1–3):11–19. [PubMed: 23454558]
- Pisani A, Sabbatini M, Riccio E, Rossano R, Andreucci M, Capasso C, De Luca V, Carginale V, et al. Effect of a recombinant manganese superoxide dismutase on prevention of contrast-induced acute kidney injury. *Clin Exp Nephrol*. 18(3):424–431.
- Plotnikov EY, Chupyrkina AA, Jankauskas SS, Pevzner IB, Silachev DN, Skulachev VP, Zorov DB. Mechanisms of nephroprotective effect of mitochondria-targeted antioxidants under rhabdomyolysis and ischemia/reperfusion. *Biochim Biophys Acta*. 2011; 1812(1):77–86. [PubMed: 20884348]
- Prakash J, de Borst MH, Lacombe M, Opdam F, Poelstra K, Kok RJ, et al. Inhibition of renal rho kinase attenuates ischemia/reperfusion-induced injury. *J Am Soc Nephrol*. 2008; 19(11):2086–2097. [PubMed: 18650485]
- Quiros Y, Sánchez-González PD, López-Hernández FJ, Morales AI, López-Novoa JM. Cardioprotrophin-1 administration prevents the renal toxicity of iodinated contrast media in rats. *Toxicol Sci*. 2013; 132(2):493–501. [PubMed: 23335628]
- Rajan D, Wu R, Shah KG, Jacob A, Coppa GF, Wang P. Human ghrelin protects animals from renal ischemia-reperfusion injury through the vagus nerve. *Surgery*. 2012; 151(1):37–47. [PubMed: 21943641]

- Ramesh G, Reeves WB. TNF-alpha mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. *J Clin Invest*. 2002; 110(6):835–842. [PubMed: 12235115]
- Rasbach KA, Schnellmann RG. Isoflavones promote mitochondrial biogenesis. *J Pharmacol Exp Ther*. 2008; 325(2):536–543. [PubMed: 18267976]
- Rosner MH. Acute kidney injury in the elderly. *Clin Geriatr Med*. 2013; 29(3):565–578. [PubMed: 23849008]
- Rostami B, Nematbakhsh M, Pezeshki Z, Talebi A, Sharifi MR, Moslemi F, Eshraghi-Jazi F, Ashrafi F. Effect of testosterone on Cisplatin-induced nephrotoxicity in surgically castrated rats. *Nephrourol Mon*. 2014; 6(5):e21546. [PubMed: 25695037]
- Sahu BD, Kuncha M, Sindhura GJ, Sistla R. Hesperidin attenuates cisplatin-induced acute renal injury by decreasing oxidative stress, inflammation and DNA damage. *Phytomedicine*. 2013; 20(5):453–460. [PubMed: 23353054]
- Salom MG, Cerón SN, Rodríguez F, López B, Hernández I, Fenoy FJ, et al. Heme oxygenase-1 induction improves ischemic renal failure role of nitric oxide and peroxynitrite. *Am J Physiol Heart Circ Physiol*. 2007; 293(6):H3542–H3549. (Salom et al., 2007). [PubMed: 17890422]
- Samarasinghe DA, Tapner M, Farrell GC. Role of oxidative stress in hypoxia-reoxygenation injury to cultured rat hepatic sinusoidal endothelial cells. *Hepatology*. 2000; 31(1):160–165. [PubMed: 10613741]
- Satake A, Takaoka M, Nishikawa M, Yuba M, Shibata Y, Okumura K, Kitano K, Tsutsui H, Fujii K, Kobuchi S, Ohkita M, Matsumura Y. Protective effect of 17beta-estradiol on ischemic acute renal failure through the PI3K/Akt/eNOS pathway. *Kidney Int*. 2008; 73(3):308–317. [PubMed: 18004295]
- Schneider MP, Sullivan JC, Wach PF, Boesen EI, Yamamoto T, Fukai T, Harrison DG, Pollock DM, Pollock JS. Protective role of extracellular superoxide dismutase in renal ischemia/reperfusion injury. *Kidney Int*. 2010; 78(4):374–381. [PubMed: 20505656]
- Semenza GL. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. *Annu Rev Pathol*. 2014; 9:47–71. [PubMed: 23937437]
- Sener G, Tu tepe H, Yüksel M, Cetinel S, Gedik N, Ye en BC. Resveratrol improves ischemia/reperfusion-induced oxidative renal injury in rats. *Arch Med Res*. 2006; 37(7):822–829. [PubMed: 16971220]
- Shah KG, Rajan D, Jacob A, Wu R, Krishnasastri K, Wang P, et al. Attenuation of renal ischemia and reperfusion injury by human adrenomedullin and its binding protein. *J Surg Res*. 2010; 163(1):110–117. [PubMed: 20538296]
- Sharfuddin AA, Sandoval RM, Berg DT, McDougal GE, Campos SB, Phillips CL, Jones BE, Gupta A, Grinnell BW, Molitoris BA. Soluble thrombomodulin protects ischemic kidneys. *J Am Soc Nephrol*. 2009; 20(3):524–534. [PubMed: 19176699]
- Sharples EJ, Yaqoob MM. Erythropoietin and acute renal failure. *Semin Nephrol*. 2006; 26(4):325–331. [PubMed: 16949472]
- Shimizu H, Takahashi T, Suzuki T, Yamasaki A, Fujiwara T, Akagi R, et al. Protective effect of heme oxygenase induction in ischemic acute renal failure. *Crit Care Med*. 2000; 28(3):809–817. [PubMed: 10752834]
- Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury a new class of renoprotective agents [J]. *Transplantation*. 1998; 66(2):147–152. [PubMed: 9701255]
- Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G. Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. *Am J Med*. 1987; 83(1):65–71.
- Si J, Ge Y, Zhuang S, Wang LJ, Chen S, Gong R. Adrenocorticotrophic hormone ameliorates acute kidney injury by steroidogenic-dependent and -independent mechanisms. *Kidney Int*. 2013; 83(4):635–646. [PubMed: 23325074]
- Simmons MN, Subramanian V, Crouzet S, Haber GP, Colombo JR Jr, Ukimura O, Nielsen S, Gill IS. Alpha-melanocyte stimulating hormone analogue AP214 protects against ischemia induced acute kidney injury in a porcine surgical model. *J Urol*. 2010; 183(4):1625–1629. [PubMed: 20172543]
- Singh D, Chander V, Chopra K. Protective effect of catechin on ischemia-reperfusion-induced renal injury in rats. *Pharmacol Rep*. 2005; 57(1):70–76. [PubMed: 15849379]

- Singh D, Chopra K. The effect of naringin, a bioflavonoid on ischemia-reperfusion induced renal injury in rats. *Pharmacol Res.* 2004; 50(2):187–193. [PubMed: 15177308]
- Sogabe K, Roeser NF, Venkatachalam MA, Weinberg JM. Differential cytoprotection by glycine against oxidant damage to proximal tubule cells. *Kidney Int.* 1996; 50(3):845–854. [PubMed: 8872959]
- Sohotnik R, Nativ O, Abbasi A, Awad H, Frajewicki V, Abassi Z, et al. Phosphodiesterase-5 inhibition attenuates early renal ischemia-reperfusion-induced acute kidney injury assessment by quantitative measurement of urinary NGAL and KIM-1. *Am J Physiol Renal Physiol.* 2013; 304(8):F1099–F1104. [PubMed: 23364806]
- Soljancic A, Ruiz AL, Chandrashekar K, Maranon R, Liu R, Reckelhoff JF, Juncos LA. Protective role of testosterone in ischemia-reperfusion-induced acute kidney injury. *Am J Physiol Regul Integr Comp Physiol.* 2013; 304(11):R951–R958. [PubMed: 23552495]
- Su HC, Hung LM, Chen JK. Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab.* 2006; 290(6):E1339–E1346. [PubMed: 16434553]
- Sutton TA, Kelly KJ, Mang HE, Plotkin Z, Sandoval RM, Dagher PC. Minocycline reduces renal microvascular leakage in a rat model of ischemic renal injury. *Am J Physiol Renal Physiol.* 2005; 288(1):F91–F97. [PubMed: 15353401]
- Suzuki S, Maruyama S, Sato W, Morita Y, Sato F, Miki Y, Kato S, Katsuno M, Sobue G, Yuzawa Y, Matsuo S. Geranylgeranylacetone ameliorates ischemic acute renal failure via induction of Hsp70. *Kidney Int.* 2005; 67(6):2210–2220. [PubMed: 15882264]
- Szakaly P, Laszlo E, Kovacs K, Racz B, Horvath G, Ferencz A, Lubics A, Kiss P, et al. Mice deficient in pituitary adenylate cyclase activating polypeptide (PACAP) show increased susceptibility to in vivo renal ischemia/reperfusion injury. *Neuropeptides.* 2011; 45(2):113–121. [PubMed: 21211837]
- Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng FY, Zhao Z, Ganger M, Tow CY, Seshan SV. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. *J Am Soc Nephrol.* 2011; 22(6):1041–1052. [PubMed: 21546574]
- Tanaka R, Tsutsui H, Kobuchi S, Sugiura T, Yamagata M, Ohkita M, Takaoka M, Yukimura T, Matsumura Y. Protective effect of 17 β -estradiol on ischemic acute kidney injury through the renal sympathetic nervous system. *Eur J Pharmacol.* 2012; 683(1–3):270–275. [PubMed: 22426161]
- Tang C, Dong Z. Epigenetic regulation in acute kidney injury: new light in a dark area. *Kidney Int.* 2015; 88(4):665–668. [PubMed: 26422622]
- Tang J, Liu N, Tolbert E, Ponnusamy M, Ma L, Gong R, Bayliss G, Yan H, Zhuang S. Sustained activation of EGFR triggers renal fibrogenesis after acute kidney injury. *Am J Pathol.* 2013; 183(1):160–172. [PubMed: 23684791]
- Tang J, Yan Y, Zhao TC, Gong R, Bayliss G, Yan H, Zhuang S. Class I HDAC activity is required for renal protection and regeneration after acute kidney injury. *Am J Physiol Renal Physiol.* 2014; 307(3):F303–F316. [PubMed: 24808536]
- Tang J, Zhuang S. Epigenetics in acute kidney injury. *Curr Opin Nephrol Hypertens.* 2015; 24(4):351–358. [PubMed: 26050122]
- Tang J, Liu N, Zhuang S. Role of epidermal growth factor receptor in acute and chronic kidney injury. *Kidney Int.* 2013; 83(5):804–810. [PubMed: 23325080]
- Toda N, Takahashi T, Mizobuchi S, Fujii H, Nakahira K, Akagi R, et al. Tin chloride pretreatment prevents renal injury in rats with ischemic acute renal failure. *Crit Care Med.* 2002; 30(7):1512–1522. [PubMed: 12130972]
- Tögel F, Zhang P, Hu Z, Westenfelder C. VEGF is a mediator of the renoprotective effects of multipotent marrow stromal cells in acute kidney injury. *J Cell Mol Med.* 2009; 13(8B):2109–2114. [PubMed: 19397783]
- Tögel FE, Westenfelder C. Mesenchymal stem cells a new therapeutic tool for AKI. *Nat Rev Nephrol.* 2010; 6(3):179–183. [PubMed: 20186233]
- Trionfini P, Benigni A, Remuzzi G. MicroRNAs in kidney physiology and disease. *Nat Rev Nephrol.* 2015; 11(1):23–33. [PubMed: 25385286]

- Tu tepe H, Sener G, Biyikli NK, Yüksel M, Cetinel S, Gedik N, Ye en BC. The protective effect of oxytocin on renal ischemia/reperfusion injury in rats. *Regul Pept.* 140(3):101–108.
- Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med.* 2006; 34(7):1913–1917. [PubMed: 16715038]
- Valverde P, Benedito ESolano F, Oaknin S, Lozano JA, Garcia Borron JC. Melatonin Antagonizes α -Melanocyte-Stimulating Hormone Enhancement of Melanogenesis in Mouse Melanoma Cells by Blocking the Hormone-Induced Accumulation of the C Locus Tyrosinase. *Eur J Biochem.* 1995; 232(1):257–263. [PubMed: 7556159]
- Venkatachalam MA, Weinberg JM, Kriz W, Bidani AK. Failed Tubule Recovery, AKI-CKD Transition, and Kidney Disease Progression. *J Am Soc Nephrol.* 2015; 26(8):1765–1776. [PubMed: 25810494]
- Venkatachalam MA, Weinberg JM, Patel Y, Saikumar P, Dong Z. Cytoprotection of kidney epithelial cells by compounds that target amino acid gated chloride channels. *Kidney Int.* 1996; 49(2):449–460. [PubMed: 8821829]
- Wada Y, Iyoda M, Matsumoto K, Shindo-Hirai Y, Kuno Y, Yamamoto Y, Suzuki T, Saito T, Iseri K, Shibata T. Epidermal growth factor receptor inhibition with erlotinib partially prevents Cisplatin-induced nephrotoxicity in rats. *PLoS One.* 2014; 9:e111728. [PubMed: 25390346]
- Wang J, Wei Q, Wang CY, Hill WD, Hess DC, Dong Z. Minocycline up-regulates Bcl-2 and protects against cell death in mitochondria. *J Biol Chem.* 2004; 279(19):19948–19954. [PubMed: 15004018]
- Wang J, Wei Q, Wang CY, Hill WD, Hess DC, Dong Z. Minocycline up-regulates Bcl-2 and protects against cell death in mitochondria. *J Biol Chem.* 2004; 279(19):19948–19954. [PubMed: 15004018]
- Wang X, Bonventre JV, Parrish AR. The aging kidney increased susceptibility to nephrotoxicity. *Int J Mol Sci.* 2014; 15(9):15358–15376. [PubMed: 25257519]
- Wang Y, Pei DS, Ji HX, Xing SH. Protective effect of a standardized Ginkgo extract (ginaton) on renal ischemia/reperfusion injury via suppressing the activation of JNK signal pathway. *Phytomedicine.* 2008; 15(11):923–931. [PubMed: 18929474]
- Wang Z, Havasi A, Gall J, Bonegio R, Li Z, Mao H, Schwartz JH, Borkan SC. GSK3 β promotes apoptosis after renal ischemic injury. *J Am Soc Nephrol.* 2010; 21(2):284–294. [PubMed: 20093356]
- Watanabe M, de Moura Neiva LB, da Costa Santos CX, Martins Laurindo FR, de Fátima Fernandes Vattimo M. Isoflavone and the heme oxygenase system in ischemic acute kidney injury in rats. *Food Chem Toxicol.* 45(12):2366–2371.
- Watanabe T, Tanaka M, Watanabe K, Takamatsu Y, Tobe A. Research and development of the free radical scavenger edaravone as a neuroprotectant [Article in Japanese]. *Yakugaku Zasshi.* 2004; 124(3):99–111. [PubMed: 15049127]
- Wei Q, Bhatt K, He HZ, Mi QS, Haase VH, Dong Z. Targeted deletion of Dicer from proximal tubules protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol.* 2010; 21(5):756–761. [PubMed: 20360310]
- Wei Q, Hill WD, Su Y, Huang S, Dong Z. Heme oxygenase-1 induction contributes to renoprotection by G-CSF during rhabdomyolysis-associated acute kidney injury. *Am J Physiol Renal Physiol.* 2011; 301(1):F162–F170. [PubMed: 21511696]
- Weidemann A, Bernhardt WM, Klanke B, Daniel C, Buchholz B, Câmpean V, Amann K, Warnecke C, Wiesener MS, Eckardt KU, Willam C. HIF activation protects from acute kidney injury. *J Am Soc Nephrol.* 2008; 19(3):486–494. [PubMed: 18256363]
- Wen X, Peng Z, Li Y, Wang H, Bishop JV, Chedwick LR, Singbartl K, Kellum JA. One dose of cyclosporine A is protective at initiation of folic acid-induced acute kidney injury in mice. *Nephrol Dial Transplant.* 2012; 27(8):3100–3109. [PubMed: 22294776]
- Xiao T, Guan X, Nie L, Wang S, Sun L, Zhao J, et al. Rapamycin promotes podocyte autophagy and ameliorates renal injury in diabetic mice. *Mol Cell Biochem.* 2014; 394(1–2):145–154. [PubMed: 24850187]

- Xiao X, Hu Y, Quirós PM, Wei Q, López-Otín C, Dong Z. OMA1 mediates OPA1 proteolysis and mitochondrial fragmentation in experimental models of ischemic kidney injury. *Am J Physiol Renal Physiol*. 306(11):F1318–F1326.
- Xu Y, Ma H, Shao J, Wu J, Zhou L, Han J, et al. A Role for Tubular Necroptosis in Cisplatin-Induced AKI. *J Am Soc Nephrol*. 2015; 26(11):2647–2658. [PubMed: 25788533]
- Yamashita J, Ogata M, Takaoka M, Matsumura Y. KB-R7943, a selective Na⁺/Ca²⁺ exchange inhibitor, protects against ischemic acute renal failure in mice by inhibiting renal endothelin-1 overproduction. *J Cardiovasc Pharmacol*. 2001; 37(3):271–279. [PubMed: 11243417]
- Yang D, Yang D, Jia R, Tan J. Na⁺/Ca²⁺ exchange inhibitor, KB-R7943, attenuates contrast-induced acute kidney injury. *J Nephrol*. 2013; 26(5):877–885. [PubMed: 23475466]
- Yasuda H, Kato A, Miyaji T, Zhou H, Togawa A, Hishida A. Insulin-like growth factor-I increases p21 expression and attenuates cisplatin-induced acute renal injury in rats. *Clin Exp Nephrol*. 2004; 8(1):27–35. [PubMed: 15067513]
- Yasuda H, Yuen PS, Hu X, Zhou H, Star RA. Simvastatin improves sepsis-induced mortality and acute kidney injury via renal vascular effects. *Kidney Int*. 2006; 69(9):1535–1542. [PubMed: 16557230]
- Yasuda K, Ozaki T, Saka Y, Yamamoto T, Gotoh M, Ito Y, Yuzawa Y, Matsuo S, Maruyama S. Autologous cell therapy for cisplatin-induced acute kidney injury by using non-expanded adipose tissue-derived cells. *Cytherapy*. 2012; 14(9):1089–1100. [PubMed: 22731757]
- Yen TH, Alison MR, Goodlad RA, Otto WR, Jeffery R, Cook HT, Wright NA, Poulsom R. Epidermal growth factor attenuates tubular necrosis following mercuric chloride damage by regeneration of indigenous, not bone marrow-derived cells. *J Cell Mol Med*. 2015; 19(2):463–473. [PubMed: 25389045]
- Yeung BHY, Wong CKC. Stanniocalcin-1 Regulates Re-Epithelialization in Human Keratinocytes. *PLoS ONE*. 2011; 6:e27094. [PubMed: 22069492]
- Yoon HY, Kang NI, Lee HK, Jang KY, Park JW, Park BH. Sulforaphane protects kidneys against ischemia-reperfusion injury through induction of the Nrf2-dependent phase 2 enzyme. *Biochem Pharmacol*. 2008; 75(11):2214–2223. [PubMed: 18407246]
- Yoshida T, Kumagai H, Kohsaka T, Ikegaya N. Relaxin protects against renal ischemia reperfusion injury. *Am J Physiol Renal Physiol*. 2013; 305(8):F1169–F1176. [PubMed: 23946288]
- Yoshida T, Kumagai H, Kohsaka T, Ikegaya N. Protective effects of relaxin against cisplatin-induced nephrotoxicity in rats. *Nephron Exp Nephrol*. 2014; 128(1–2):9–20. [PubMed: 25403022]
- Zhou D, Tan RJ, Lin L, Zhou L, Liu Y. Activation of hepatocyte growth factor receptor, c-met, in renal tubules is required for renoprotection after acute kidney injury. *Kidney Int*. 2013; 84(3):509–520. [PubMed: 23715119]
- Zhuang S, Lu B, Daubert RA, Chavin KD, Wang L, Schnellmann RG. Suramin promotes recovery from renal ischemia/reperfusion injury in mice. *Kidney Int*. 2009; 75(3):304–311. [PubMed: 18843260]
- Zhuang S, Schnellmann RG. Suramin promotes proliferation and scattering of renal epithelial cells. *J Pharmacol Exp Ther*. 2005; 314(1):383–390. [PubMed: 15833899]
- Zuk A, Gershenovich M, Ivanova Y, MacFarland RT, Fricker SP, Ledbetter S. CXCR4 antagonism as a therapeutic approach to prevent acute kidney injury. *Am J Physiol Renal Physiol*. 2014; 307(7):F783–F797. [PubMed: 25080523]

Fig. 1.

Overview of renoprotective approaches in acute kidney injury. Insults, such as ischemia/reperfusion, sepsis, and various nephrotoxins, induces injury and death of renal tubular cells, vascular dysfunction, and inflammation, resulting in acute kidney injury and renal failure. Renoprotective agents may protect tubular cells, suppress inflammatory response, and/or maintain renal vasculature in AKI.

Fig. 2.
Experimental strategies for identifying renoprotective approaches for AKI: from rodent to mammalian models

Fig. 3.
Experimental strategies for identifying renoprotective approaches for AKI: from single to multiple models

Fig. 4.
Experimental strategies for identifying renoprotective approaches for AKI: from AKI-only to comorbid models

Table 1

Clinical drugs with renoprotective effects in AKI

No	Name	Characteristics	Tested AKI model	Mechanism
1	Leflunomide	Pyrimidine synthesis inhibitor used in immunosuppressive diseases such as rheumatoid arthritis and psoriatic arthritis	IRI in rat	reduce oxidative stress
2	Etanercept	TNF- α inhibitor used to treat autoimmune diseases	IRI in rat	lower expression of TNF- α and MCP-1
3	Statins drugs	Inhibitors of HMG-CoA reductase used to lower cholesterol	drug-, septic- and ischemic -induced AKI in rat or mice	antioxidant, anti-inflammatory and anti-apoptotic
4	Edaravone	Neuroprotective agent in acute brain ischemia and subsequent cerebral infarction	IRI in rats	increase Bcl-2 expression
5	Paricalcitol	Analog of vitamin D2 active form, VDR agonist	IRI in male C57BL/6 mice	upregulate COX-2 and PGE2
6	Tadalafil, Sildenafil	Phosphodiesterase type 5 inhibitor	contrast-induced AKI in rabbits	Inhibit protein kinase G
7	Milrinone	Phosphodiesterase type 3 inhibitor	IRI in mice	Inhibit NF- κ B activation
8	Fidarestat	Aldose reductase inhibitor for diabetic complications	LPS-induced endotoxic AKI	suppress inflammation
9	Telmisartan	Angiotensin II receptor antagonist used in hypertension	IRI in rats	decrease MDA, TNF- α , NO and homocysteine
10	Adrenomedullin	A potent endogenous vasodilatory peptide hormone	contrast induced AKI in rats	negative regulation of the RAAS
11	Rituximab	Monoclonal antibody against CD20 used in autoimmunity	IRI in mice	Suppression of inflammation
12	Cyclosporin A	Immunosuppressant used in transplant medicine	FA-induced AKI in mice	block TWEAK expression and NF- κ B activation
13	Mycophenolate mofetil	Immunosuppressant used in transplant or autoimmune diseases	IRI in rats	attenuate the increase of cytokines RANTES and AIF
14	Temsirolimus	Inhibitor of mammalian target of rapamycin (mTOR)	septic-AKI in older adult mice	induce autophagy
15	Doxycycline	Tetracycline antibiotics for treating infections or inflammation	IRI in a rat model of ACS	decrease IL-1 β , TNF- α and MMP-2
16	suramin	An antiparasitic drug used in treatment of trypanosomiasis	IRI in mice	reduce tubular apoptosis and infiltrating leukocytes
17	Geranylgeranylacetone	An antiulcer drug used in treatment of gastric ulcers	IRI in rats	induction of Hsp70

Table 2

Herbs, food and dietary nutrients with renoprotective effects in AKI

No	Name	Characteristics	Tested AKI model	Mechanism
1	Korean Red Ginseng	Perennial plants belonging to genus <i>Panax</i> of the Araliaceae	AKI by cisplatin and gentamicin in rat	reduce OS and inflammation
2	<i>Radix Codonopsis</i> (saponins)	Perennial plants used frequently in traditional Chinese medicine	IRI after kidney transplant in rat	decrease lipid peroxidation and inhibit apoptosis
3	<i>artemisia asiatica</i>	Wormwood, traditional uses include treating liver problems, joint pain, gastric reflux	IRI in male C57BL/6 mice	increase the level of HO-1 and Bcl-2
4	Ginkgo extract (ginkatone)	Herb extracts used for treating Alzheimer's disease, memory loss, headache, et al.	IRI in rats	suppress extrinsic apoptotic pathway induced by JNK
5	naringin (flavonoids)	A flavonoid in grapefruit metabolized to flavanone naringenin	IRI in rats	reduce TBARS, restore antioxidant enzymes
6	quercetin (flavonoids)	A pigment with a molecular structure like or derived from flavone	IRI in rats	increase GSH levels and activities of SOD and CAT
7	hesperidin (flavonoids)	A flavanone glycoside found abundantly in citrus fruits	cisplatin-induced AKI in rats	attenuate OS, inflammation, apoptosis/necrosis
8	curcumin (Flavonoids)	A diarylheptanoid which is a member of the ginger family	IRI in rats	attenuate expression of RANTES, MCP-1
9	Catechin (Flavanols)	Derivatives of flavans that are abundant in teas	IRI in rats	similar to naringin in rat kidney
10	Resveratrol (Polyphenols)	A phenol found in red grapes, Japanese knotweed, etc	septic-AKI in mice IRI in rats glycerol-ARF in rats cisplatin-AKI in mice	Antioxidant, release NO, activate SIRT1 and inhibit p53
11	Astragaloside IV	Marker compound in <i>Astragali Radix</i>	IRI in rats	inhibit OS and p38 MAPK phosphorylation
12	Sulforaphane	A molecule within isothiocyanate from cruciferous vegetables	H/R in HK2 RPTC IRI in mice	induce Nrf2-dependent phase 2 enzymes
13	Sesame oil	Extraction from sesame seeds containing Vit E, Vit B6, etc	AAs and contrast-induced AKI in rats	inhibit renal OS
14	Polyenylphosphatidylcholine	A lecithin soybean extract	IRI in rats	reduce levels of AST, BUN and NF- κ B
15	Isoflavones	Phytoestrogens (plant estrogens) isolated from the soybean	IRI in rats	induce heme oxygenase

Table 3

Other chemicals with renoprotective effects in AKI

No	Name	Characteristics	Tested AKI model	Mechanism
1	N-acetylcysteine	A precursor of the antioxidant glutathione	AKI by contrast in human, various AKI models in mouse and rat	reduce oxidative stress
2	Glutamine	The abundant free amino acid in human blood while conditionally essential in states of illness or injury	folic acid-induced AKI in CD-1 mice glycerol-induced AKI in rat	inhibit JNK phosphorylation and enhancing Hsp70
3	Glycine	The smallest amino acids found in proteins or natural products	ATP-depleted MDCK cells, Menadione-induced injury of RPTC	target amino acid gated chloride channels
4	rMnSOD	MnSOD recombinant generated by DNA technique	contrast-induced AKI in rat	reduce renal oxidative stress
5	TDZD-8	Pharmacological inhibitor of GSK3 β	ATP-depleted BUMPT cells, IRI in rats	inhibit activation of GSK3 β , Bax, and caspase 3
6	Nutlin-3	Small molecule antagonist of MDM2	Cisplatin-induced rat RPTC apoptosis	suppress the activation of Bax/Bak
7	Minocycline	Semisynthetic derivative of tetracycline	hypoxia, et al-RPTC apoptosis, IRI in rats	induction of Bcl-2
8	Mdivi-1	Selective cell-permeable inhibitor of mitochondrial fission protein DRP1	Azide, cisplatin-RPTC apoptosis, IRI in C57BL/6 mice	attenuate mitochondrial fragmentation and apoptosis
9	OMA1	Mediator of mitochondrial inner membrane cleavage	ATP-depleted RPTC, IRI in C57BL/6 mice	mediate OPA1 proteolysis and mitochondrial fragmentation
10	SS-31	Synthetic cell-permeable tetrapeptide that targets and concentrates in mitochondrial inner membrane	IRI in rats	protect mitochondria by interacting with cardiolipin
11	SkQR1	Cationic rhodamine derivative linked to a plastoquinone molecule	glycerol-, IR-induced AKI in rats	inhibit MPP and scavenge ROS
12	SRT1720	Selective SIRT1 activator	IRI in rats	activate PGC-1 α for mitochondrial biogenesis
13	Formoterol	Specific β 2-adrenergic agonist	IRI in mice	promote mitochondrial biogenesis and recovery
14	sotrastaurin	Selective pan-PKC inhibitor	kidney transplantation in rat	inhibit the induced PKC in transplantation
15	Y27632	Coupled to lysozyme, selective Rho kinase inhibitor	IRI in rats	reduce KIM-1, vimentin, MCP-1
16	zafirlukast	Antagonist of CysLT1R	IRI in rats	reduce neutrophil infiltration, P-selectin overexpression
17	Necrostatin-1	Specific inhibitor of RIP1 kinase	contrast-induced AKI in mice	prevent dilation of peritubular capillaries

No	Name	Characteristics	Tested AKI model	Mechanism
18	KB-R7943	Inhibitor of Na ⁺ / Ca ²⁺ exchange	IRI in mice contrast-induced AKI in rat	suppress the increased ET-1 and catalase

Table 4**Hormones with renoprotective effects in AKI**

No	Name	Characteristics	Tested AKI model	Mechanism
1	17 β -estradiol	The primary female hormone	Ischemic AKI in mouse, rat	activate PI3K/Akt/eNOS pathway, suppress renal SNS
2	Relaxin	A hormone of insulin superfamily exists in ovary and breast of female or prostate and semen of male	IRI in rats cisplatin-induced AKI in rat	decrease plasma TNF- α levels and renal TNFR1
3	Oxytocin	A neurohypophysial hormone stimulating uterine contraction during and after childbirth	IRI in rats	decrease TNF- α and oxidative damage
4	AQGV	An oligopeptide related to the primary structure of beta-hCG	IRI in mice	decrease TNF- α , INF- γ , IL-6 and IL-10
5	Testosterone	A androgen hormone secreted primarily by testicles	IRI in rats	attenuate the increase of urinary KIM-1 and intrarenal TNF- α
6	α -MSH	Hormones causing increased pigmentation, named as Melanocortins	ischemic AKI in mice and rats	suppress neutrophil activation and infiltration
7	ACTH		septic AKI of cecal ligation puncture	induce MC1R-mediated anti-apoptotic effect,
8	AP214		septic AKI in mice, ischemic AKI in a porcine	reduce NF-kB and splenocyte apoptosis
9	Melatonin	the physiological antagonist of α -MSH	ischemic AKI in C57Bl/6N mice	improve the migration and survival of eEPCs
10	Ghrelin	The hunger hormone produced in the gastrointestinal tract	IRI in rats	decrease kidney IL-6 and MPO activity, increase Bcl-2/Bax ratio
11	STC-1	A hormone regulating renal calcium/phosphate homeostasis	IRI in mice	activate AMPK induce UCP-2 of mitochondria
12	PACAP	A hypophysiotropic hormone similar to vasoactive intestinal peptide	IRI in rats	prevent Bcl-2 decrease and apoptotic effects
13	Dexamethasone	An artificial synthetic of Glucocorticoid hormone	septic AKI in C57BL/6 mice	reduce MD with preserved COI

Table 5

Cytokines, growth factors and gene-interfered with renoprotective effects in AKI

No	Name	Characteristics	Tested AKI model	Mechanism
1	IL-10	cytokine synthesis inhibitory factor	Ischemic- and cisplatin- AKI in the mouse	reduce levels of TNF- α , ICAM-1, and iNOS
2	CXCR ₄ antagonist	Plerixafor, a small-molecule antagonist of CXCR ₄	IRI in rats	reduce chemokines CXCL1, CXCL5 and IL-6
3	TNF- α inhibition	Inhibitors of TNF- α production (GM6001, pentoxifylline), anti-TNF- α antibody, specific TNF- α knockout	cisplatin- AKI in Swiss-Webster mice	decrease levels of TNF- α , TGF- β , RANTES, MIP-2, MCP-1, and IL-1 β
4	ICAM-1 inhibition	Specific ICAM-1 knockout, Anti-ICAM-1 antibody	IRI in mice IRI in rats	attenuate neutrophil endothelial interactions
5	CT-1	A member of IL-6 family and a potent pleiotropic cytokine	contrast-induced AKI in rats	prevent tubular desepithelization and obstruction
6	NGAL	A member of the lipocalin super family with diverse function	IRI in rats	inhibit activation of caspase-3 and expression of Bax
7	L-FABP	A member of intracellular lipid-binding proteins involved in the transportation of fatty acids	AA-induced AKI in mice	suppress the production of HEL, HO-1, and receptor for AGEs
8	sTM	A glycoprotein present on the membrane surface of endothelial cells in many organs, including lung, liver, and kidney.	IRI in rats	improve microvascular erythrocyte flow rates
9	COMP-Ang1	A soluble and potent Ang1 variant, act as the ligand for Tie2 tyrosine kinase receptor that is expressed on EC.	unilateral ureteral obstruction-induced renal fibrosis	improve peritubular capillary and enhance renal tissue (re)perfusion
10	IGF	A hormone similar in molecular structure to insulin	IRI in rats cisplatin- RPTC cisplatin- or HgCl ₂ - AKI in mice	ameliorate acute tubular necrosis; produce pro-survival factor IGF-1
11	MFG-E8	A protein involved in marking apoptotic cells for phagocytosis	IRI in C57BL/6 mice	suppress renal inflammation
12	EGF	A potent growth promoter to renal tubule cells, produced in large amounts in the kidney	HgCl ₂ - AKI in mice	attenuate tubular necrosis
13	EGFR inhibitor	erlotinib, a selective tyrosine kinase inhibitor that can block EGFR activity	cisplatin- AKI in rats	decrease apoptosis and proliferation of tubular cells
14	HGF	A potent mitogen for parenchymal liver, epithelial and endothelial cells, as a ligand of MET oncoprotein	glycerol-, gentamicin- AKI in rats	attenuate tubulointerstitial injury, leukocyte infiltration and Th1 polarization
15	EPO	Glycoprotein produced by the kidney that regulates red blood cell production in the bone marrow	IR-, cisplatin- and contrast- AKI in mice or rats or pigs	inhibit apoptosis and promote cellular regeneration
16	G-CSF	Glycoprotein that stimulates bone marrow to produce granulocytes and stem cells	glycerol- AKI In C57BL/6 mice	induction of HO-1
17	NF- κ B Blockade	NF- κ B decoy oligodeoxynucleotides; NF- κ B inhibitor milrinone, resveratrol	IRI in rats or mice	decrease MCP-1 expression and

No	Name	Characteristics	Tested AKI model	Mechanism
				monocyte infiltration
18	HIF-1	Ubiquitously expressed hypoxia-inducible transcription factor	IR- or cisplatin- in rats	ameliorate tubulointerstitial and vascular damage
19	HIF-2	Hypoxia-inducible transcription factor mainly expressed on endothelial cells	IRI in mice	protect from vascular damage and fibrosis
20	PKC δ knockdown	A member of PKC subfamily involved in cell apoptosis	cisplatin- AKI in mice, cisplatin-RPTCs	Activated MAPKs for apoptosis and tissue damage
21	OMA1 knockdown	a zinc metalloprotease located at mitochondrial inner membrane that is involved in mitochondrial inner membrane disruption in cell stress	ATP-depleted RPTC, IRI in C57BL/6 mice	mediate OPA1 proteolysis and mitochondrial fragmentation
22	Dicer deletion	A key ribonuclease for microRNA production, Dicer deletion leads to a global downregulation of microRNAs	IRI in mice	depletion of the majority of microRNAs
23	miR-687, -24 blockade	endogenous, noncoding, small RNAs that regulate expression and function of genes	hypoxia-induced RPTC injury / apoptosis, IRI in mice	attenuate cell cycle activation and apoptosis
24	miR-127, -34a, -155, -126 blockade			ameliorate histologic tubular damage, apoptosis