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The multifaceted role of the renal microvasculature during acute kidney injury

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Abstract

Pediatric acute kidney injury (AKI) represents a complex disease process for clinicians as it is multifactorial in cause and only limited treatment or preventatives are available. The renal microvasculature has recently been implicated in AKI as a strong therapeutic candidate involved in both injury and recovery. Significant progress has been made in the ability to study the renal microvasculature following ischemic AKI and its role in repair. Advances have also been made in elucidating cell–cell interactions and the molecular mechanisms involved in these interactions. The ability of the kidney to repair post AKI is closely linked to alterations in hypoxia, and these studies are elucidated in this review. Injury to the microvasculature following AKI plays an integral role in mediating the inflammatory response, thereby complicating potential therapeutics. However, recent work with experimental animal models suggests that the endothelium and its cellular and molecular interactions are attractive targets to prevent injury or hasten repair following AKI. Here, we review the cellular and molecular mechanisms of the renal endothelium in AKI, as well as repair and recovery, and potential therapeutics to prevent or ameliorate injury and hasten repair.

Keywords

Acute kidney injury; Microvasculature; Endothelium; Immune response; Tissue hypoxia; Ischemia reperfusion injury

Introduction

Acute kidney injury (AKI) is characterized as a rapid (hours to days) decrease in kidney function [1]. AKI is one of the most serious and common health complications, occurring in up to 20 % of all hospitalized patients and over 45 % of patients in critical care settings [2, 3]. While not well defined in children, the incidence of AKI in pediatric intensive care units is reported to range from 8 to 30 % and occurs in roughly 7 % of the general pediatric

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population [4–6]. The incidence of AKI in children appears to be increasing, and the etiology over the past decades has shifted from primary renal disease to multi-factorial causes, particularly in hospitalized children. An important cause of AKI in hospitalized children is the setting of post-cardiac surgery and stem cell transplantation [7]. Pharmacotherapy is also one of the major causes of AKI and may play a causative role in as many as 25 % of all pediatric cases [6, 8]. Drugs, including antimicrobials, chemotherapeutic agents, and non-steroidal anti-inflammatory drugs, among others, have all been implicated in drug-induced renal injury in children [5]. Severe sepsis with shock, use of vasopressors along with invasive ventilation, fluid overload, and tumor lysis syndrome also contribute to the numbers of AKI seen in children [9]. In newborns, the incidence of AKI in the USA is 3.9 per 1000 live births and 34.5 per 1000 newborns admitted to the neonatal unit [7, 10]. Several genetic factors may also predispose some children to AKI [7]. As the kidney is a highly vascularized organ, the complex vasculature is extremely sensitive to damage during AKI. The role that the complex microvasculature system plays during AKI events remains vastly understudied. Subtle malformations in kidney vasculature development could leave the kidneys at significant risk of further insults.

Microvascular development and the role of Foxd1 during AKI

Kidney development involves interactions between the metanephric mesenchyme and the ureteric epithelium [11–13]. The metanephric mesenchyme subdivides into the nephrogenic mesenchyme and the renal stroma [14]. As the kidney develops, the renal stroma interdigitates between the nephron progenitor caps, and the ureteric bud branches to form primary renal interstitium [11, 15]. The renal stroma eventually gives rise to many of the vascular supportive cells (including pericytes, fibroblasts, renin-producing cells, and mesangium), as well as to endothelial progenitors [11, 16, 17]. The kidney receives approximately 20 % of the cardiac output through its vasculature system [17, 18]. The vascular system begins with the growth and invagination (angiogenesis) of new blood vessels. At the same time, resident endothelial precursors, within the kidney mesenchyme, form primitive vascular structures (vasculogenesis) that eventually connect with the angiogenic vessels to form a patent vascular system. The exact combination of angiogenesis and vasculogenesis that contributes to the formation of the kidney vasculature is unclear. In an earlier study, our laboratory showed that a subset of the renal endothelium derived from the renal stroma (marked by the Foxd1 gene) gave rise to peritubular capillaries [16]. Foxd1 is a transcription factor in the stromal cells and is the earliest identifier of the renal stroma [11, 18]. Kidneys with a Foxd1 deletion display severe structural deformities [11, 19] as well as reduced branching of the ureteric bud, decreased number of nephrons, abnormalities of the renal capsule, misplaced vasculature in the renal capsule, and overall aberrant patterning of renal structures [11, 19, 20]. Foxd1 has recently been shown to participate in the proper orientation of the kidney vasculature [18]. When the kidney is subjected to injury models [unilateral ureteral obstruction or ischemia–reperfusion injury (IRI)], it is the Foxd1-derived cells that contribute to the fibrotic response [21–47] (Table 1). Our laboratory is currently investigating the role of the Foxd1-derived endothelium in determining susceptibility to AKI.

Ischemic reperfusion AKI

There are many different causes of pediatric AKI; however, hypoxic/ischemic AKI will be the focus of this review. IRI leading to AKI is characterized by early vasoconstriction followed by patchy tubular necrosis. Mild to moderate acute ischemic injury results in epithelial injury and death, although the renal tubules can repair following injury. However, severe or multiple ischemic injury events cause incomplete repair resulting in fibrogenesis [24] (Fig. 1). Part of the work carried out in our laboratory has focused on the relative tissue hypoxia following ischemic AKI in mice using pimonidazole hydrochloride (Hypoxyprobe™-1). Hypoxyprobe™-1 is activated in hypoxic cells and forms covalent adducts with sulphydryl groups within the tissue. Immunostaining of kidneys for hypoxyprobe, as well as for the endothelial marker endomucin 24 h post unilateral IRI was performed, and hypoxic tissues were visualized (Fig. 2). The kidney receives approximately 25 % of the cardiac output, however it is also one of the most naturally hypoxic organ systems. Oxygen tensions in the renal parenchyma are lower than that in most other organs, with the renal medulla considered an area with one of the lowest oxygen tensions [25, 26]. Twenty-four hours following IRI, a significant amount of hypoxic tissue was visible, and it was especially prevalent around the renal tubules compared to the contralateral control kidney (Fig. 2a, b). The pathophysiology of IRI in the kidney is very complex, with many pathological pathways implicated, including activation of neutrophils and the release of reactive oxygen species and other inflammatory mediators, including adhesion molecules and cytokines [27]. In response to hypoxia, inflammatory, renal tubular epithelial cells, and vascular cells secrete thrombospondin-1 (TSP1), which is a matricellular glycoprotein [22, 23, 48, 49]. TSP1 binds to the cell surface receptor CD47 to regulate the canonical nitric oxide (NO) pathway, which is suppressed in IRI [29, 49–51]. Several therapies have mitigated IRI through NO supplementation [49, 52–55]. Furthermore, Rogers et al. demonstrated that limiting CD47 activation prevents TSP1 binding and reduces complications of renal IRI in mice, providing a potential therapeutic intervention [49] (Table 1).

Recent studies suggest that the renal vasculature plays a role in acute and chronic injury. Furthermore, the endothelial cells have been identified as a target of injury and potential for therapeutics. The peritubular capillaries, which comprise the arterial portal system derived from the efferent arteriole, supply adjacent tubules in the cortex and renal medulla [28]. During AKI, peritubular capillary blood flow is abnormal during reperfusion, and this is accompanied by loss of endothelial cell function in association with distorted peritubular capillary morphology and function [7, 30, 56]. Moreover, pediatric patients following ischemic AKI have a high predisposition to progressive renal failure and hypertension, [30–32], while injury in the setting of transplantation (i.e., delayed graft function) represents an independent risk factor for graft survival and the development of post-transplant hypertension [31, 57]. These observations suggest that ischemic acute injuries to the kidney predispose to chronic complications.

Kidney microvasculature and AKI

The kidney contains one of the most diverse and rich populations of endothelial cells within the body [58]. Tubular epithelial cell injury is linked to AKI. However, unlike the renal tubules, the kidney microvasculature lacks regenerative capacity following severe or multiple AKI events [24, 31, 59]. Renal injury may directly damage the renal vasculature and alter its activity; such damage may influence vascular responsiveness, barrier function, coagulation cascades, and/or inflammatory processes [33, 56, 60]. Early alterations in peritubular capillary blood flow during reperfusion is linked with the loss of endothelial cell function [59]. Capillary loss, which alters renal function and predisposes patients to the development of chronic renal insufficiency, is due in part to hypoxia [30, 59]. Inflammation and procoagulant activity, which contribute to vascular congestion, are also induced by hypoxia/ischemia [59]. Several significant studies suggest that altered renal endothelial function contributes to a reduction in renal blood flow following AKI [34]. Arrerio and colleagues propagated endothelial like cells from mesenchymal stem cells; these cells expressed markers typical of endothelial cells such as Tie-2 (an angiopoietin receptor), vascular endothelial growth factor receptors (VEGFR) 1 and 2, and endothelial nitric oxide synthase 3 (eNOS3). Prophylactic injection of these cells to control rats generated short-term engraftment into the vasculature and short-term protection from AKI [35]. These studies suggest that endothelial function may have protective effects on AKI. Dimke and colleagues recently determined that VEGF-A is highly expressed in renal tubular epithelial cells, allowing tubulovascular cross-talk to its receptor (VEGFR2) which is located almost exclusively to peritubular capillary endothelial cells. Using a genetic approach to excise VEGF-A from the renal tubules, the authors demonstrated a substantial reduction in peritubular capillary density upon its removal. VEGF-A is deemed necessary and critical for maintenance of the peritubular microvasculature by directing tubulovascular cross-talk with the VEFGR2-expressing endothelial cells. This implicates a physiologic role of tubular VEGF-A in mediating cross-talk between the tubular system and the vasculature in the kidney [61]. Several studies have provided further evidence supporting endothelial cell/tubule cell cross-talk. It has been elegantly demonstrated that proximal tubule cells release cytokines and chemokines in response to cell injury and that these agents have direct effects on endothelial function [36, 37, 62, 63].

Adenosine plays an important role in the kidney by regulating renin release, glomerular filtration rate (GFR), and renal vascular tone [64, 65], while also playing a critical role in the regulation of tubular glomerular feedback [64–66]. During pathological insults to the kidney, adenosine levels increase due to renal ATP consumption, impaired renal perfusion, and hypoxia [65]. Grenz and colleagues demonstrated how adenosine provides protection against ischemic AKI in mouse models by preserving peritubular capillary blood flow during reperfusion. These authors showed that adenosine activation of endothelial Adora2b results in less tissue hypoxia and improved reperfusion [38, 44].

With damage to the microvasculature leading to capillary loss following AKI, fibrogenesis and capillary rarefaction progress, which induces focal hypoxia activating an injury, cascade leading to inflammation, and continued fibrosis [24, 67, 68]. The damaged or dysfunctional renal endothelium is often characterized by an impaired dilator capacity, which can be

attributed to reduced production of NOS3 [39]. Unfortunately, it is unclear whether vasodilators can work to correct this impaired dilator capacity, as the endothelial tissue injury prevents vasodilator therapy from generating the desired effects [34]. Several studies have demonstrated that infusing endothelial cells with NOS3 gene expression constructs help to protect against early compromised blood flow in the peritubular capillaries caused by ischemic AKI, thereby supporting the positive effects of NOS3 on endothelial function [33–35] (Table 1). Following endothelial damage during AKI, the majority of normal renal function can be restored. However, hypoxic areas may remain, which can alter sodium reabsorption [69]. Furthermore, an increased expression of hypoxia inducible factor-1α (HIF-1α) and HIF-2α has been found in AKI. The role of these HIFs in the pathogenesis of AKI was unclear until recently [70]. Kapitsinou and colleagues utilized a genetic approach to inactivate both HIF-1α and HIF-2α in the renal endothelium, where they found that the HIF-2α isoform in the renal endothelium was critical for protection from AKI (Table 1) [70]. Until recently, microvascular damage following AKI was assessed through examination of the surface area of endothelial cells, or visualization of the capillaries [24, 40–42], through immunostaining and genetic labeling of the endothelium. Advani and colleagues were able to develop a fluorescence microangiography technique by renal artery injection in rats [71]. This technique was refined by Kramaan and colleagues and utilized in a mouse model of AKI to evaluate the microvasculature; they also generated a sophisticated MATLAB-based script for high-throughput analysis of the microvascular changes [24] (Table 1). This methodology to evaluate the renal endothelium will be invaluable to understand microvasculature alterations.

Renal ischemic injury alters the cytoskeletal organization of small arterioles and endothelial cells that may relate to the presentation of surface expression molecules. This disruption in cellular morphology may also disrupt endothelial cell tight junctions, resulting in endothelial leakiness. Endothelial leakiness can cause an increase in edema and compromise renal perfusion [56, 72, 73]. The loss of endothelial cell function may represent an important therapeutic target in which vascular trophic support and/or endothelial regeneration by progenitor cells ameliorate the acute and chronic effects of ischemic AKI [74].

Immune response to AKI is mediated by endothelial cells

In addition to the myriad of altered vascular functions that influence AKI progression, inflammation is mediated in part by the adhesion of leukocytes to damaged endothelial cells [75]. Following AKI, tissue damage initiates an inflammatory cascade including reactive oxygen species (ROS), cytokines, chemokines, and leukocytes [27, 43, 76].

In combination with endothelial adhesiveness, inflammatory mediators are synthesized and released by both tubular epithelial cells (one of the primary sites of damage) and activated leukocytes. Tubular epithelial cells produce tumor necrosis factor-alpha, interleukin (IL)-1, IL-6, IL-8, transforming growth factor beta, monocyte chemotactic protein 1 (MCP-1), ENA78, RANTES and fractalkines, while leukocytes produce IL-1, IL-8, MCP-1, ROS, and eicosanoids. These factors act in concert to promote inflammation in a positive feedback loop, promoting further kidney injury [75, 77]. The endothelium is also a source of chemoattractant factors, such as fractalkine (CX3CL1), which is expressed following renal

injury and promotes macrophage infiltration [75]. Numerous studies conducted over the past two decades have revealed that inflammatory processes mediated by the immune system are crucial in mediating renal injury [78, 79]. Both innate and adaptive immune systems are directly involved in the pathogenesis of ischemic AKI. Various cellular and humeral immune system components contribute to AKI, some of which are also thought to be involved in the repair process following AKI [76, 79, 80]. Resident macrophages in normal kidneys are few, while in post-ischemic kidneys (especially in the outer medulla), directly following IRI, their number markedly increases [79, 81]. Monocytes then adhere to the vasa recta 2 h after reperfusion, while most macrophage recruitment occurs around post-capillary venules in the outer medulla [79, 82]. Chemokines are also direct mediators of chemotaxis and activation of immune cells; specifically, they guide neutrophils and pro-inflammatory (M1) macrophages to the injury site [83, 84]. M1 macrophages amplify the inflammatory response and promote tissue damage following AKI. Over time (days) M1 macrophages are replaced by alternatively activated M2 macrophages that promote repair [85–87]. The mechanisms that regulate these macrophage phenotypes remain poorly understood. Chiba and colleague's recently demonstrated that retinoic acid (RA) is able to regulate macrophage activation following AKI through suppressing M1 macrophages and indirectly inducing M2 macrophages, thereby enhancing post-AKI repair [86] (Table 1). Neutrophils, which are important effector cells of the innate immune system, then phagocytose pathogens and particles, generate reactive oxygen and nitrogen species, and release antimicrobial peptides. Neutrophil infiltration has been detected in post-ischemic mouse kidneys [88, 89] and in biopsy samples from patients with early AKI [90, 91]. Neutrophils are, therefore, expected to play an important role in the pathogenesis of IRI [79]. Intra-renal activation of HIFs following AKI occurs in tubular, interstitial, and endothelial cells. Upregulation of HIF-1α occurs within 1 h and is sustained for up to 7 days; it induces the infiltration of macrophages following IRI [79, 92]. Mechanical interruption of renal vascular endothelial integrity caused by IRI, and the consequent increase in vascular permeability is another factor that facilitates infiltration of immune cells into the post-ischemic kidney [33, 72, 79]. Furthermore, endothelial cell dysfunction is thought to contribute to the failure of blood to re-perfuse an ischemic area after removal of any physical obstruction (termed the 'no-reflow' phenomenon) in post-ischemic kidneys [79].

Therapeutic intervention

As the number of AKI patients continues to grow, so has the interest in therapeutic interventions. However, due to the complex and multifaceted nature of AKI, successful treatment or prevention will involve cellular, molecular, and immune processes. Appropriate therapeutics for AKI will most likely involve targeting the endothelium and renal tubule cells to minimize injury, as well as mediating the immune response [37]. Studies are currently being conducted to modulate the involvement of immune infiltrating cells in AKI in order to limit their associated damage [37, 93]. Most immune invading cells are detrimental, but some, such as regulatory T cells (Tregs), are beneficial [37, 94–96], and enhancing Tregs using IL-2 complexes has been shown to reduce histologic injury and improve function in mice [37, 97].

Endothelial dysfunction has been shown to be one of the earliest pathological sequences following AKI [98, 99]. When endothelial cells are damaged during AKI, they undergo apoptosis, which further amplifies the coagulation cascade [37, 100]. This cascade leads to enhanced microvascular coagulation and endothelial cell dysfunction. Ultimately, microvascular function is compromised, and local tissue perfusion is decreased. Pretreatment or post-injury treatment with soluble thrombomodulin (TM) attenuates ischemic AKI by reducing vascular permeability defects and minimizing white blood cell–endothelial interactions, and thus improves microvascular perfusion [37, 101]. Ischemic injury leads to the release of many cytokines that downregulate the expression of TM, hence causing a state of relative TM deficiency, leaving the microvasculature in a pro-coagulant state [43, 102]. TM has now been well established to possess beneficial roles in inflammation, fibrinolysis, apoptosis, cell adhesion, and cellular proliferation [45, 46, 101, 103].

Selective inhibition, depletion, or deletion of inducible NOS (iNOS) has also clearly shown renoprotective effects during ischemia [37, 47, 104]. It has been proposed that with a relative decrease in endothelial NOS (eNOS), secondary to endothelial dysfunction and damage, there is a loss of antithrombogenic properties of the endothelium, leading to increased susceptibility to microvascular thrombosis [37, 105]. Administration of the L-arginine nitric oxide (NO) donor molsidomine or the eNOS cofactor tetrahydrobiopterin can preserve medullary perfusion and attenuate IRI-induced AKI; conversely, the administration of *N*-nitro-L-arginine methyl ester, an NO blocker, has been reported to aggravate the course of AKI following IRI [37, 106, 107].

It is not clear yet whether apoptosis and necrosis play a major role in endothelial cell dropout. Ischemia has been shown to inhibit the angiogenic protein vascular endothelial growth factor (VEGF), while inducing the putative VEGF inhibitor ADAMTS-1 [37, 108]. It has been postulated that the lack of vascular repair could be due to VEGF deficiency, as shown by experiments where the administration of VEGF-121 preserved microvascular density [37, 109].

In a recent study, Pabla and colleagues provided evidence that the CDK4/6 (cyclin-dependent kinases) pathway is activated early during AKI and demonstrated significant protective effects of CDK4/6 inhibitors in animal models of cisplatin-induced AKI. In addition, these authors found that the CDK4/6 inhibitors palbociclib and LEE011 are potent inhibitors of organic cation transporter 2 (OCT2), a cisplatin uptake transporter highly expressed in renal tubular cells [110–113]. Their findings provide a rationale for the clinical development of palbociclib and LEE011 for the prevention and treatment of AKI (Table 1).

Fairly recently, micoRNAs (miRNAs) have emerged as potential biomarkers useful in AKI risk assessment, diagnosis, prognosis, and severity of injury [114]. miRNAs are highly conserved and are essential for normal development and physiology [114]. Lorenzen and colleagues identified 13 miRNAs with differential regulation between AKI and healthy control patients [115]. The authors proceed to describe miR-210, a miRNA known to be upregulated in endothelial cells in association with tissue hypoxia and upregulated in patients with AKI [116, 117], and miR-320 and miR-16, both downregulated, as potential

biomarkers. Cantaluppi and colleagues suggest that miRNAs such as miR-126 and miR-296, which are derived from microparticles in circulating endothelial progenitor cells, may ameliorate the effects of AKI [118, 119]. While the research on miRNAs in AKI is still limited, these molecules hold much promise as a potential therapeutic application.

Notably, despite the high prevalence and mortality rates of AKI, no clinically proven therapeutic interventions are available to prevent it [120]. While many laboratories are working on possible treatments or preventatives for AKI, a significant amount of pre-clinical studies are required to test efficacy.

Conclusion

In conclusion, this review highlights the role of the renal microvasculature in AKI. We have highlighted the many causes of AKI while focusing on those related to ischemic injury (as described in Fig. 1; [121]). Furthermore, this review examines the molecular and cellular mechanisms that currently exist and have been elegantly studied in murine models. The study of the renal microvasculature during AKI may provide a critical therapeutic window that ultimately will enable prevention of this widespread disease.

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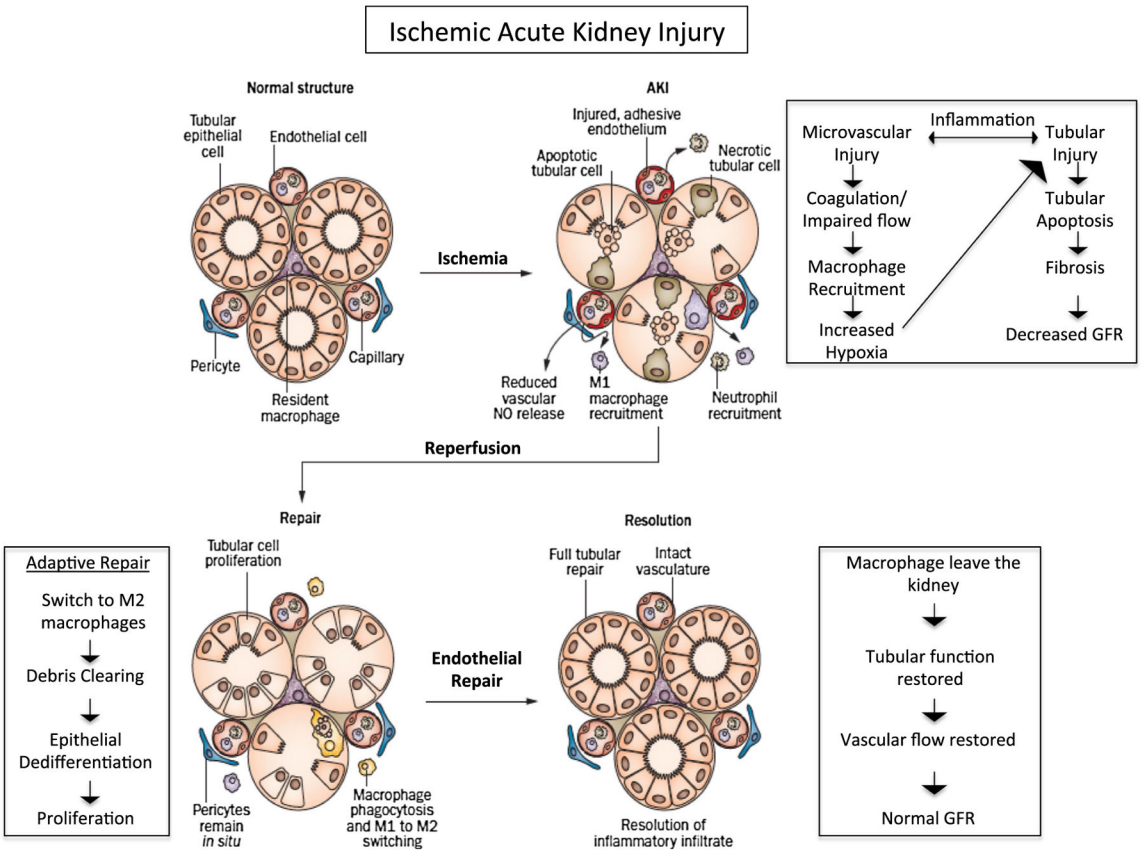

Fig. 1.

Injury, repair, and resolution during ischemic acute kidney injury (*AKI*). Following ischemia, there is substantial microvascular injury, leading to increased coagulation, reduced nitric oxide release, macrophage recruitment, and increased hypoxia. These events in turn lead to significant tubular injury and death, ultimately causing a decrease in glomerular filtration rate (*GFR*). Following reperfusion, the kidney enters adaptive repair in which inflammation and debris begins to resolve through a switch from M1 macrophages to M2 macrophages. Both endothelial repair and epithelial tubular proliferation begin, leading to resolution. Adapted from Fernenback and Bonventre [121] with permission from Macmillan Publishers Ltd

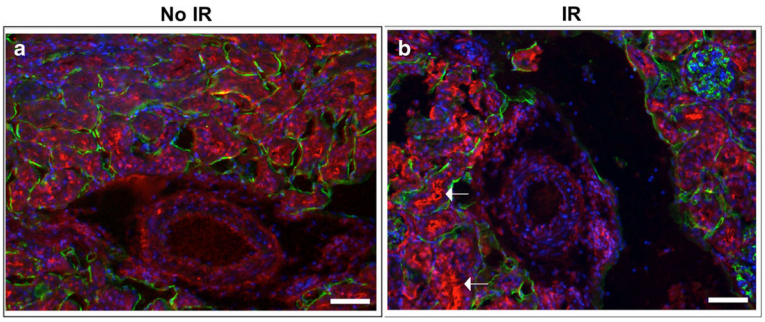

Fig. 2.

Hypoxic markers are present following ischemic reperfusion injury. **a**, **b** Hypoxyprobe- (*red*) and endomucin- (*green*) stained kidneys 1 day following 20 min of unilateral ischemic reperfusion injury (*IR*) (**b**), and the contralateral controls (**a**). One day following injury, ischemic kidneys (**b**) display markedly more hypoxic tubules (*arrows*) when compared with the contralateral control (**a**). *Scale bars*:100 μm

Table 1

Important findings implicating renal endothelium in acute kidney injury

Major findings	Implications	Authors
During AKI, peritubular capillary blood flow is reduced, and morphology is distorted, as well as loss of endothelial cell function	The vasculature of the kidney plays a role in injury and progression to chronic disease. The endothelium may be a potential target for therapeutics	Andreoli et al. (2009) [7]; Sutton et al. (2002) [22]; Basile et al. (2007) [23]
TSP1 is found to bind to CD47 and acts to suppress the NO pathway following IRI	Supplementation of NO mitigates IRI	Isenburg et al. (2007) [21]; Martinez-Mier et al. (2000) [24]; Rodriguez-Pena et al. (2004) [25]; Liu et al. (2007) [26]; Lang et al. (2007) [27]
Limiting CD47 activation prevents TSP1 binding in mice.	Mitigates the complications of IRI providing a potential therapeutic	Rogers et al. (2012) [18]
A subset of the renal endothelium derived from the renal stroma (marked by Foxd1) gives rise to peritubular capillaries	Foxd1 gives rise to vasculogenic endothelium and contributes to a fibrotic response following AKI	Sims-Lucas et al. (2013) [28]; Hum et al. (2014) [29]; Sequeira-Lopez et al. (2015) [30]; Levinson et al. (2005) [31]; Hatini et al. (1996) [32]
Renal endothelial functions contributes to a reduction in renal blood flow following AKI. NOS3 has positive effects on renal endothelial function	Enhanced endothelial function may have protective effects on AKI	Brodsky et al. (2002) [33]; Basile et al. (2014) [34]; Arriero et al. (2004) [35]
Following AKI, hypoxic areas remain after normal function is restored. Furthermore, HIF-2α is critical for protection in AKI	HIFs are implicated as taking part in the pathogenesis of AKI	Ergin et al. (2015) [36]; Kapitisinou et al. (2015) [37]
A fluorescence microangiography technique is established for visualization if the microvasculature	An invaluable technique to understand microvasculature alterations	Advani et al. (2011) [38]; Kramann et al. (2014) [11]
Inflammatory processes mediated by the immune system are crucial in mediating renal injury	Targeting inflammation may be a potential therapeutic for AKI	Basile et al. (2012) [39]; Bonventre et al. (2004) [40]; Gonclaves et al. (2010) [41]; Jang et al. (2015) [42]
Using retinoic acid, M1 macrophages can be suppressed, indirectly inducing M2 macrophages to enhance repair following AKI	Administration of retinoic acid following AKI enhances repair	Chiba et al. (2015) [43]
Endothelial cell dysfunction may contribute to the failure of blood to reperfuse an ischemic area	Further implicates endothelial cells as a possible target for therapeutic intervention	Brodsky et al. (2002) [33]; Sutton et al. (2003) [44]; Jang et al. (2015) [42]
CDK4/6 is activated early during AKI, and displays protective effects of CDK4/6 inhibitors in animal models of AKI	Rational for the clinical development of CDK4/6 inhibitors for the prevention and treatment of AKI	Flipski et al. (2009) [45]; Ciarimboli et al. (2010) [46]; Sprowl et al. (2014) [47]

AKI, Acute kidney injury; IRI, ischemia–reperfusion injury; NO, nitric oxide; NOS3, nitric oxide synthase 3; HIF-2α, hypoxia inducible factor-2 alpha; CDK4/6, cyclin-dependent kinase 4/6