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Immune Mechanisms and Novel Pharmacological Therapies of Acute Kidney Injury

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Abstract

Ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury (AKI) and both innate and adaptive immunity contribute to the pathogenesis. Kidney resident cells promote inflammation after IRI by increasing endothelial cell adhesion molecule expression and vascular permeability. Kidney epithelial cells bind complement and express tolllike receptors and resident and infiltrating cells produce cytokines/chemokines. Early activation of kidney dendritic cells (DCs) initiates a cascade of events leading to accumulation of interferon-γ-producing neutrophils, infiltrating macrophages, $CD4^+$ T cells, B cells and invariant natural killer T (NKT) cells. Recent studies from our laboratory now implicate the IL23/IL17 pathway in kidney IRI. Following the initial early phase of inflammation, the late phase involves infiltration of anti-inflammatory cells including regulatory T cells, alternatively activated macrophages and stem cells leading to attenuation of inflammation and initiation of repair. Based upon these immune mechanisms of injury, recent studies hold promise for novel drug therapies. These pharmacological agents have been shown to reduce inflammation or cytotoxicity in rodent models of AKI and some show early promise in clinical trials. This review summarizes recent advances to further our understanding of the immune mechanisms of AKI and potential pharmacological therapies.

Keywords

Acute renal failure; ischemia-reperfusion injury; cisplatin; inflammation

Introduction

Effective therapy of acute kidney injury (AKI) especially in critically ill patients remains elusive. Mortality in these patients is alarmingly high despite substantial advances in techniques of resuscitation and renal replacement therapy. The incidence of AKI is increasing markedly [1,2] as a result of the expansion of invasive medical and surgical procedures and the increasing expectation for aggressive medical management of critically ill patients. In critically ill patients, mortality is 40-60% [3-6] and traditionally attributed to comorbid conditions. Accumulating data suggests, however, that AKI has an independent negative impact on mortality [7,8]. The success of therapeutic interventions for AKI necessitates a better understanding of its pathogenesis. Inflammation plays a critical role in AKI and the following review discusses immune mechanisms contributing to injury and repair associated with AKI as well a novel therapeutics.

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Overview of Experimental Acute Kidney Injury

AKI is a consequence of vasospasm, alterations in ultrafiltration coefficient, tubular obstruction and/or back-leak [9,10]. Renal ischemia-reperfusion (IR) is a major cause of AKI. The mechanisms involved in renal ischemia-reperfusion injury (IRI) are complex [9,11], invoking both innate and adaptive immunity [12,13]. Following IR, the cascade of events leading to endothelial cell dysfunction, tubular epithelial cell injury and activation of tissue-resident and infiltrating leukocytes consists of the coordinated action of cytokines/chemokines, reactive oxygen intermediates and adhesion molecules [11,13]. The early phase of innate immune response to IR begins within minutes of reperfusion, whereas the late phase adaptive response requires days to manifest.

Early Phase Inflammation in Ischemia-Reperfusion Injury

Ischemia and/or reperfusion initiate changes in vascular endothelial cells, tubular epithelial cells (TEC) and resident renal dendritic cells (DCs) that cause the loss of immune system homeostasis in the kidney (see recent reviews [13-15]). As a result, numerous pro-inflammatory leukocytes are attracted to, and are activated within the post-ischemic kidney, potentiating the direct damage inflicted on kidney parenchymal cells by IR.

Endothelial Cells

Activation of the endothelium following kidney IRI leads to a loss of vascular endothelial cell integrity [16,17] and up-regulation of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1) and P-selectin [18-20] that facilitate leukocyte-endothelial cell interactions. Macrophages expressing CX_3CR1 and CCR2 are recruited by endothelial cells leading to the production of chemokines mediating their recruitment into the injured kidney [21,22]. Therefore, the endothelium, which serves as the interface between immune cells and the renal parenchyma is a highly reactive tissue involved in the early phase of inflammation and kidney damage by promoting the accumulation of leukocytes.

Epithelial Cells

Epithelial cells contribute to inflammation and early kidney injury following IR. The basolateral membrane of proximal tubule cells express the complement inhibitor, Crry [23]. After renal IR, Crry is internalized allowing the deposition of complement component 3 (C3) on the tubular epithelium [23], complement activation and production of the pro-inflammatory chemokines macrophage inflammatory factor-2 (MIP-2) and keratinocyte-derived chemokine (KC) [24]. These chemokines attract neutrophils and macrophages to the post-ischemic kidney. In addition, toll-like receptors (TLR) 2 and 4 are up-regulated in epithelial cells after IR and deficiency of either TLR on kidney parenchymal cells was more effective at preventing kidney IRI than TLR deficiency on bone marrow derived cells [25,26]. TLR2 or TLR4 deficiency blunted the IR-induced production of proinflammatory cytokines and chemokines and inhibited macrophage and neutrophil accumulation. These studies highlight the important role for renal epithelial cells in the inflammation of AKI.

Resident Kidney Dendritic Cells (DCs)

Immature DCs are present in virtually all tissues and participate in immune surveillance. DCs are an important link between innate and adaptive immunity and their role in AKI has only recently been investigated. $CD11c^+$ and class II major histocompatibilty complex (MHC Class $II)^+$ DCs are the most abundant leukocyte subset in the normal mouse kidney [22,27] suggesting an important role in renal immunity and inflammation. In the normal C57BL/6 mouse kidney analyzed by 4 color FACS, all of the kidney $F4/80^{high}$ cells are $CD11c^+$ and these cells also express CD86, MHC class II^{high} and CX_3CR1, indicating that these cells have a DC phenotype

[22]. Mature DCs are specialized for T cell activation. However, DCs can also initiate the innate immune response presenting endogenous glycolipids and stimulating NKT cells [28]. After IR, renal DCs produce the pro-inflammatory cytokines/chemokines TNF-α, IL-6, MCP-1 and RANTES, and depletion of DCs prior to IRI significantly reduced the kidney levels of TNF-α, [29]. IL-12 and IL-23 are mainly produced from activated DCs and macrophages, and their downstream cytokines, IFN-γ and IL-17, amplify the immune response following kidney reperfusion through macrophage activation and neutrophil recruitment (personal communication L Li and MD Okusa 2009).

Non-Resident Bone Marrow-Derived Cells

Non-resident bone marrow-derived cells, such as neutrophils [11,13-15,30,31] macrophages [32,33], natural killer cells [34], T cells [14,35,36] and natural killer T cells [28] rapidly infiltrate the kidney during reperfusion, in response to the signals from resident renal cells and in a distinct temporal profile [22]. A brief summary of the role of these leukocytes in the pathogenesis of renal IRI follows.

Neutrophils—Neutrophils rapidly respond to injury and are important mediators of innate immunity. Neutrophils release granules containing proteases and other enzymes, which generate reactive oxygen species. In inflammatory states, neutrophil degranulation can lead to the destruction of normal self cells in the inflamed tissue. One of the hallmarks of renal IRI is neutrophil accumulation in the post-ischemic kidney [18,26,28,37] and depletion of neutrophils prevents AKI [18].

Macrophages—Macrophages are derived from monocytes [38-40] in the blood and have heterogeneous functions [13,40-42]. Macrophages also produce pro-inflammatory cytokines that can stimulate the activity of other leukocytes. Macrophages infiltrate the injured kidney early within 1 hour of reperfusion, and this infiltration is mediated by CCR2 [22] and CX_3CR1 signaling pathways [21,22]. These macrophages have a distinct $F4/80^{low}Ly6C^{high}GR1^{+}CX_3CR1^{low}$ "inflamed" phenotype [22] and through depletion and transfer studies macrophages have been documented to contribute to kidney IRI [32]. Analysis of kidney infiltrating macrophages by flow cytometry demonstrated that these leukocytes are significant producers of the cytokines IL-1α, IL-6, IL-12p40/70 and TNF-α [22].

Natural Killer (NK) Cells—NK cells have recently been reported to infiltrate the post-ischemic kidney by 4 hours of reperfusion [34]. IR induced the expression of an NK cell-activating ligand (Rae-1) on TECs and *in vitro* studies demonstrated that the interaction of the NKG2D receptor on NK cells with Rae-1 on TECs causes perforin-dependent lysis of cultured kidney cells. Antibody-mediated depletion of NK cells inhibited IRI in wild-type (WT) mice and adoptive transfer of WT, but not perforin KO, NK cells into a T, B and NK cell-deficient mouse enhanced IRI.

T Lymphocytes—A role for T cells in the pathogenesis of kidney IRI has been established in different mouse models lacking certain types of lymphocytes [35,36]. In nu/nu mice (which lack $CD4^+$ and $CD8^+$ T cells), IRI measured by serum creatinine levels and renal histology, was significantly reduced compared to WT controls [36]. Reconstitution of nu/nu mice with $CD4^+$ T cells alone, but not $CD8^+$ T cells alone, restored kidney injury after IR. Additionally, Rag-1 KO mice (lacking both B and T cells) suffer less severe injury from IR and adoptive transfer of $CD4^+$ T cells from WT mice reconstitutes injury [35]. Importantly, transfer of $CD4^+$ T cells from IFN-γ KO mice failed to re-establish injury in this model [35]. These results suggest that $CD4^+$ T cells, and specifically IFN-γ produced by these cells, mediate the early phase of IRI.

Invariant Natural Killer T (iNKT) Cells—Conventional $CD4^+$ T cells are thought to play a role in antigen-specific, adaptive immunity that requires several days, a time course that cannot explain the rapid, innate immune response following IRI. NKT cells are a unique subset of T lymphocytes with surface receptors and functional properties shared with conventional T cells and NK cells. Invariant NKT cells posses a conserved invariant T cell receptor (TCR) together with the NK cell marker NK1.1. In contrast to conventional T cells, iNKT cells are activated by endogenously released glycolipid antigens. The most remarkable property of iNKT cells is their ability to rapidly produce large quantities of cytokines, including Th1-type (IFN-γ, TNF-α) and Th2-type (IL-4, IL-13), at the same time, within 1-2 hours of activation. A recent finding from our laboratory is that the number of IFN-γ producing iNKT cells in the kidney is significantly increased by 3 hours of reperfusion compared to sham-operated mice [28]. Blockade of NKT cell activation with the anti-CD1d mAb, NKT cell depletion with an anti-NK1.1 mAb in WT mice, or use of iNKT cell deficient mice ($J\alpha18^{-/-}$) inhibited the accumulation of IFN-γ producing neutrophils after IRI and prevented AKI [28]. These results demonstrate the important contribution of iNKT cells in kidney IRI.

Late Phase Inflammation and Repair in Ischemia-Reperfusion Injury

Compared to the early/innate response to kidney IR, less is known about the adaptive immune response. The late or adaptive immune response to specific antigens (from pathogens or dead self cells) occurs over the course of several days and includes DC maturation and antigen presentation and $CD4^+$ and $CD8^+$ T lymphocyte proliferation and activation.

Antigen Presenting Cells

Leukocytes such as DCs and macrophages play a key role in adaptive immunity by producing pro-inflammatory cytokines and in antigen presentation, although this latter process has received little attention until recently [43]. As discussed above, DCs are the most abundant leukocyte in the kidney. Upon stimulation, DCs can convert to a mature cell type characterized by high levels of MHC class II and costimulatory molecules and low phagocytic capacity. After kidney IR, DCs undergo maturational processing, migrate to the renal draining lymph nodes (LNs) and induce T cell proliferation in an antigen-specific fashion [44], implicating renal DCs in the adaptive immune response to IRI.

T Cells

T lymphocytes are major mediators of adaptive immunity. Antigen presentation by antigen presenting cells, in the presence of sufficient co-stimulation, causes expansion and activation of T cells with a T cell receptor (TCR) specific for the presented antigen. Kidney-derived DCs traffic to draining lymph nodes and activate T cells, a process that might result in local delayed kidney injury [44,45]. Recent studies demonstrate that T cells with diverse T cell repertoire induced greater IRI than T cells with restricted TCR repertoire providing evidence for activation of T cell receptors (TCR), through an antigen-dependent mechanism, in the pathogenesis of kidney IRI [43]. TCR α/β- and TCR γ/δ-deficient mice were mildly protected from IRI [46], an effect not observed by others [47]. A recent study by Ascon *et al.* demonstrated the accumulation of activated ($CD4^+CD69^+$ and $CD8^+CD69^+$) and effector-memory ($CD4^+CD44^{hi}CD62L^-$ and $CD8^+CD44^{hi}CD62L^-$) T cells in the kidney 2 and 6 weeks after ischemia [48]. However, global depletion of T lymphocytes, starting 3 days after ischemia, had no protective effect on cortex or medulla injury scores, measured 6 weeks after IRI [48]. So, at this time, a long-term pathogenic role of TCR activation has not been demonstrated conclusively.

Stem Cells

Following AKI, tissue repair may result from the proliferation of adjacent surviving dedifferentiated epithelial cells, mobilization of kidney specific stem cells which migrate to the site of regeneration, or from bone marrow derived mesenchymal or hematopoietic stem cells that gain access to the injured epithelium and differentiate into mature cells Fig. (**1**) [49]. There is evidence that kidneys possess adult stem cells [50-52] that have pluripotent potential. After tissue injury, intrinsic tissue stem cells may replace damaged tissue. Other studies have demonstrated that BM mesenchymal stem cells reduce inflammation and protect against IRI [53]. The effects were likely not due to differentiation of mesenchymal stem cells into tubular or endothelial cells, but to a paracrine effect that reduced expression of proinflammatory cytokines (e.g. IL-1β, TNF-α and IFN-γ) and inducible nitric oxide synthase and increased anti-inflammatory IL-10, basic-FGF, TGF-α and Bcl-2 in affected kidneys. BM mesenchymal stem cells limit activation of natural killer cells [54], which could attenuate IRI during the early phase. Other studies, in which antigen presentation or maturation of dendritic cells were blocked by BM mesenchymal stem cells, show that these cells might also be effective at inhibiting the late phase activation of the adaptive immune response [55]. In an elegant study, Humphreys and Bonventre generated transgenic mice in which tubular epithelial cells were labeled with beta-galactosidase or red fluorescent protein to determine the source of reparative cells [56]. Two days following IRI no “dilution” of label was observed indicating that surviving tubular epithelial cells were the predominant mechanism of repair. Thus although there is controversy as to mechanism of tissue repair, there is much excitement that the use of the appropriate progenitor cells may eventually lead to new therapies in limiting injury and repairing acutely injured kidneys.

Macrophages

Given their diverse phenotype [13,38-42], macrophages appear to participate in early stages of injury, and in the late stage repair process, following IR. Upon activation, alternative macrophages (M2) produce anti-inflammatory cytokines including IL-10 and TGF-β and also increase matrix production [57], suggesting the potential for this population of macrophages to participate in tissue repair [58]. A causal link between macrophages and repair processes was reported by Duffield *et al.* [59]. A conditional ablation system was used that takes advantage of transgenic mice expressing human diptheria toxin (DT) receptor in $CD11b^+$ cells (i.e. macrophages), which confers sensitivity to DT and permits macrophage depletion *in vivo* when DT is injected. DT treatment leads to failure in the liver repair process following liver injury [59]. Subsequently, Jang *et al.* [60] found impaired recovery from kidney IRI when macrophages were depleted following kidney IRI using liposomal clodronate. The anti-inflammatory phenotype of alternatively activated macrophages discussed above provides evidence for a role of macrophages in tissue repair processes.

Regulatory T Cells

Regulatory T (Treg) cells are lymphocytes with immunosuppressive properties. One important subset of Treg cells express CD4 and CD25 on the cell surface and the transcription factor, FoxP3 [61]. The mechanisms of suppression by Treg cells are diverse and include: production of antiinflammatory cytokines such as IL-10 or TGF-β, direct cell-cell contact or CTLA-4 mediated inhibition and production of extracellular adenosine [62]. Recently, Treg cells have been identified in normal mouse kidneys [63,64]. In WT mice, treatment with an anti-CD25 monoclonal antibody (PC61) selectively decreased kidney, spleen and blood $CD4^+$ $FoxP3^+$ Treg cell numbers by approximately 50%, five days after PC61 treatment [64]. At that time point, Treg cell deficiency potentiated kidney IRI, measured by plasma creatinine, acute tubular necrosis (ATN), neutrophil and macrophage accumulation and pro-inflammatory cytokine transcription in the kidney after 24 hr of reperfusion [64]. In lymphocyte-deficient Rag-1 KO

mice, adoptive transfer of WT, but not IL-10 KO, Treg cells blocked IR-induced inflammation and kidney injury [64]. These findings demonstrate that Treg cells can directly suppress the early innate inflammation, induced by IR, in an IL-10 dependent manner. In a different study, PC61 was administered 1 day prior to IRI, and while BUN levels and ATN scores were no different than control antibody-treated mice at 24 hr of reperfusion, the necrosis failed to resolve by 72 hr in the PC61-treated mice [65]. These results strongly support an important role of regulatory T cells during IRI and in kidney repair after IRI.

In summary, the early/innate immune response to kidney IR is well-characterized and robust, involving resident kidney cells and circulating pro-inflammatory leukocytes. While an adaptive immune response occurs, as evidenced by DC migration to kidney draining LNs and antigen presentation followed by kidney accumulation of activated and effector-memory T cells, direct evidence for antigen-dependent long-term kidney damage after IRI is currently lacking. Finally, BM mesenchymal stem cells, alternatively activated macrophages and Treg cells show promise for protecting the kidney during injury and/or facilitating kidney repair after IRI.

Drugs That Block Inflammation and Reduce Cytotoxicity in Acute Kidney Injury

Pharmacological therapy in the prevention and treatment of AKI has been largely unsuccessful despite proven benefits seen in preclinical studies. Prevention and treatment of AKI is indeed an important clinical issue as mortality in patients with AKI especially in critically ill patients remain alarmingly high despite substantial advances in techniques of resuscitation and renal replacement therapy. A number of drugs and investigational compounds appear promising in preclinical studies and promising investigational compounds are in use in clinical trials for a variety of indications including AKI. The success of these compound will necessitate an understanding of the pathogenesis of AKI so that appropriate rational therapies and combination therapies can be implemented in well designed clinical trials [66].

Spingosine 1 Phosphate (S1P) Analogs

S1P is a specific ligand for a family of G protein coupled endothelial differentiation gene (Edg) receptors (also referred to as $S1PRs_{1\text{-}5}$) that evoke diverse cellular signaling responses. S1PRs regulate different biological processes depending on their pattern of expression. S1P binds to receptors or acts as a second messenger to stimulate cell survival, inhibit cellular apoptosis, and is involved in cell adhesion and movement [67]. An S1P analog, FTY720, acts as an agonist at four S1PRs, with exception of $S1P_2R$. FTY720 binding to $S1P_1Rs$ lead to sequestration of lymphocytes in secondary lymphatic tissue [68]. In studies of kidney IRI, FTY720 or similar compounds induce lymphopenia and protect renal tissue from IRI [69,70]. With discovery of new more potent and selective S1PR analogs, like SEW2871, these selective agents will soon be available for preclinical and clinical studies [71]. A comprehensive list of S1PR analogs can be found in a review by Jo SK *et al.* [72]. Recently, in a phase II study, FTY720 reduced the number of lesions detected on magnetic resonance imaging and clinical disease activity in patients with multiple sclerosis [73].

A_{2A} Agonists and Other Adenosine Analogs

Locally produced adenosine in the kidney controls renal circulation and metabolic cellular activity [74]. Adenosine binds to receptor subtypes, which are members of the G-protein coupled receptor family that includes four subtypes: A_1-, A_{2A}-, A_{2B}- and A_3Rs [75]. Adenosine acts on these receptors in organs such as brain, heart and skeletal muscle and induces vasodilation to allow matching of oxygen delivery and work [74]. Based upon these findings, theophylline, an adenosine A_{1R} antagonist, has been used successfully in several randomized controlled studies to prevent radiocontrast-induced AKI (as reviewed in [76-78]).

Accumulating data demonstrates that selective activation of A_{2A}Rs reduces parenchymal injury in non-renal tissues including heart, liver, spinal cord, lung, and brain [79-81]. The selective A_{2AR}-agonist, ATL146e, is highly protective against kidney IRI by 70-80% [13,82, 83]. Following administration either before or immediately at the onset of reperfusion, ATL146e alone or in combination with a phosphodiesterase inhibitor reduced renal injury [84]. ATL146e is in human clinical studies for cardiac imaging and current efforts are directed toward human clinical studies in AKI. Additional studies demonstrate that strategies using A_1 agonists or A_3 blockers maybe effective in AKI [85,86].

Statins

3-Hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase inhibitors (statins) have been clinically approved for the reduction of cholesterol. Additional studies demonstrate that statins have anti-inflammatory and anti-oxidant activities that improve endothelial function, decrease platelet aggregation and procoagulant factors [87-89]. Pravastatin decreases the rise in plasma creatinine when compared to vehicle treatment without a change in plasma cholesterol levels [90]. Co-administraton of mevalonate, a product of HMG-CoA reductase, in renal IRI reversed the protective effect; demonstrating that the tissue protective effect of pravastatin was through inhibition of the mevalonate pathway. Similarly, when simvastatin was administered prior to cecal ligation puncture (CLP) induced sepsis, the rise in plasma creatinine, TNF-α and vascular permeability was attenuated [91]. In human studies, retrospective case controlled studies and registry studies found that statins reduced radiocontrast-induced AKI [92,93] whereas a recent prospective study did not find a benefit [94]. Several concerns regarding the latter studies preclude any firm conclusions based upon this study. Thus at this time statins continue to have potential for the prevention of radiocontrast nephropathy and perhaps other forms of AKI.

Fibrates

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that regulate glucose and lipid metabolism. PPAR-α is expressed in the renal proximal tubule which upon activation, hetero-dimerizes with the retinoic X receptor (RXR) and binds to PPAR response elements (PPREs) to regulate gene transcription involved in lipid metabolism [95-97]. IRI and cisplatin-induced AKI reduces kidney PPAR-α activity and inhibits peroxisomal and mitochondrial fatty acid oxidation [98-100] leading to the accumulation and cellular toxicity of oxidized long-chain fatty acids and long-chain acylcarnitines [101]. Fibrates have been shown to reduce cisplatin induced AKI [97,102]. Liver fatty acid binding protein (L-FABP) belongs to a super family of lipid-binding proteins with low molecular weight (14-15 kDa) whose transcription rate is regulated by fibrates through a PPRE located in its promoter region [103,104]. Most recently, fibrates have been shown to increase L-FAPB and decrease cisplatin-induced AKI [105]. When proximal tubule epithelial cells were exposed to cisplatin, the increase apoptosis was suppressed with bezafibrate [102]. The effect of bezafibrate to reduce apoptosis was associated with attenuation of cisplatin-induced translocation of proapoptotic Bax from the cytosol to the mitochondria, and increase in the expression of anti-apoptotic molecule Bcl-2 [102]. Furthermore, recent studies have indicated PPARs play an important role in inflammation and immunity [106]. Pretreatment of animals with WY-14, 643 (WY), a fibrate class of PPAR-α ligand ameliorated cisplatin-induced renal dysfunction and this was accompanied by suppression of NF-kB activation, cytokine/chemokine expression and neutrophil infiltration, suggesting that the protective effect of fibrates is mediated through its anti-inflammatory effect [107]. The current use of fibrates in lipid management may facilitate clinical trials in AKI.

Inducible Nitic Oxide Synthase (iNOS) Inhibitors

The role of nitric oxide and nitric oxide synthases has been extensively studied. Both *in vivo* and *in vitro* studies point toward the important role of iiNOS in mediating injury to proximal tubules [108]. Selective iNOS inhibitors are currently used in human investigation for a variety of indications.

Antioxidants and Antioxidant Enzymes

Excessive reactive oxygen species (ROS) generation, decreases in antioxidant defense, or both, are known to contribute to IRI and antioxidants that effectively remove ROS have been found to be effective against IRI. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), a potent free radical scavenger, improved survival and renal function in rats subjected to renal IRI [109]. Recently, stobadine, a novel synthetic pyridoindole antioxidant, which diminishes lipid peroxidation and protein impairment by free radical scavenging and anti-oxidant activity, has been shown to provide significant protection from IRI in rat kidneys [110].

Thrombomodulin and Activated Protein C (APC)

Proteolytic activation of protein C occurs on the endothelial cell by two membrane receptors, thrombomodulin and endothelial protein C receptors (EPCRs). Binding of thrombin to thrombomodulin on the endothelial surface promotes its anticoagulant properties by APC by the thrombin-thrombomodulin complex and is enhanced by binding of protein C to EPCR [111]. In addition, soluble thrombomodulin, independent of its ability to generate APC, reduced ischemia-reperfusion injury [112]. In this study an aortic clamp model was used; soluble thrombomodulin (sTM) not only attenuated the rise in creatinine following reperfusion, but it also improved microvascular erythrocyte flow, reduced microvascular endothelial leukocyte adhesion, and minimized endothelial permeability. A mutant, F376L, in which a point mutation was made in sTM, reduced ischemia-reperfusion injury suggesting that the protective effect of sTM is independent of its ability to generate APC.

APC, in addition to its effect on coagulation, has been shown to have direct cellular effects *via* EPCRs including: anti-inflammatory and anti-apoptotic activities leukocyte activation and stability of barrier function [111,113-118]. Through genetic engineering of wild type APC, mutants have been created that have the cytoprotective and anticoagulant activity of APC [119]. Following endotoxemia, these molecules with preserved cytoprotective properties are effective in preserving renal blood flow and attenuating acute kidney injury [119] and reducing mortality [120]. On the other hand an APC mutant with potent antithrombotic activity but minimal cytoprotection was less effective in reducing endotoxin-induced murine mortality [121]. Thus it is the hope that genetically- engineered APC mutants and thrombomodulin might yield specific agents that take advantage of selective anticoagulant and cytoprotective properties in future clinical studies of AKI from sepsis or in critically ill patients.

Erythropoietin (EPO) and EPO Derivatives

The haematopoietic factor erythropoietin (EPO) has recently been recognized to play a physiological role in the brain and other tissues. The EPO receptor is present in the glomerulus and TECs in the kidney [122]. EPO attenuates the dysfunction and histological changes associated with IRI [123] and in animal models of systemic shock and cisplatin-induced nephrotoxicity [124]. Non-hematopoietic erythropoietin analogs have shown similar benefit in experimental contrast-induced nephropathy [125]. In a pilot clinical trial, the efficacy of EPO to prevent AKI after coronary artery bypass grafting (CABG) was examined [126]. Seventy one patients scheduled for elective CABG randomly received either 300 U/kg of EPO or saline intravenously before surgery. EPO administration resulted in an incidence of AKI of

8% compared with an incidence of 29% in the placebo group (p = 0.035). These data are preliminary and provide promise for this mode of treatment for AKI.

In summary the complexity of AKI is due in part to activation of multiple overlapping and distinct temporal pathways. Inflammation (cellular and humoral) is a key mediator of AKI. Recent studies have highlighted novel immune mechanisms contributing to AKI that provide the foundation for newer classes of pharmacological agents that block inflammation. It is likely that new strategies to treat or prevent AKI will require drugs that target multiple pathways, or combination of drugs that targets several areas, rather than one.

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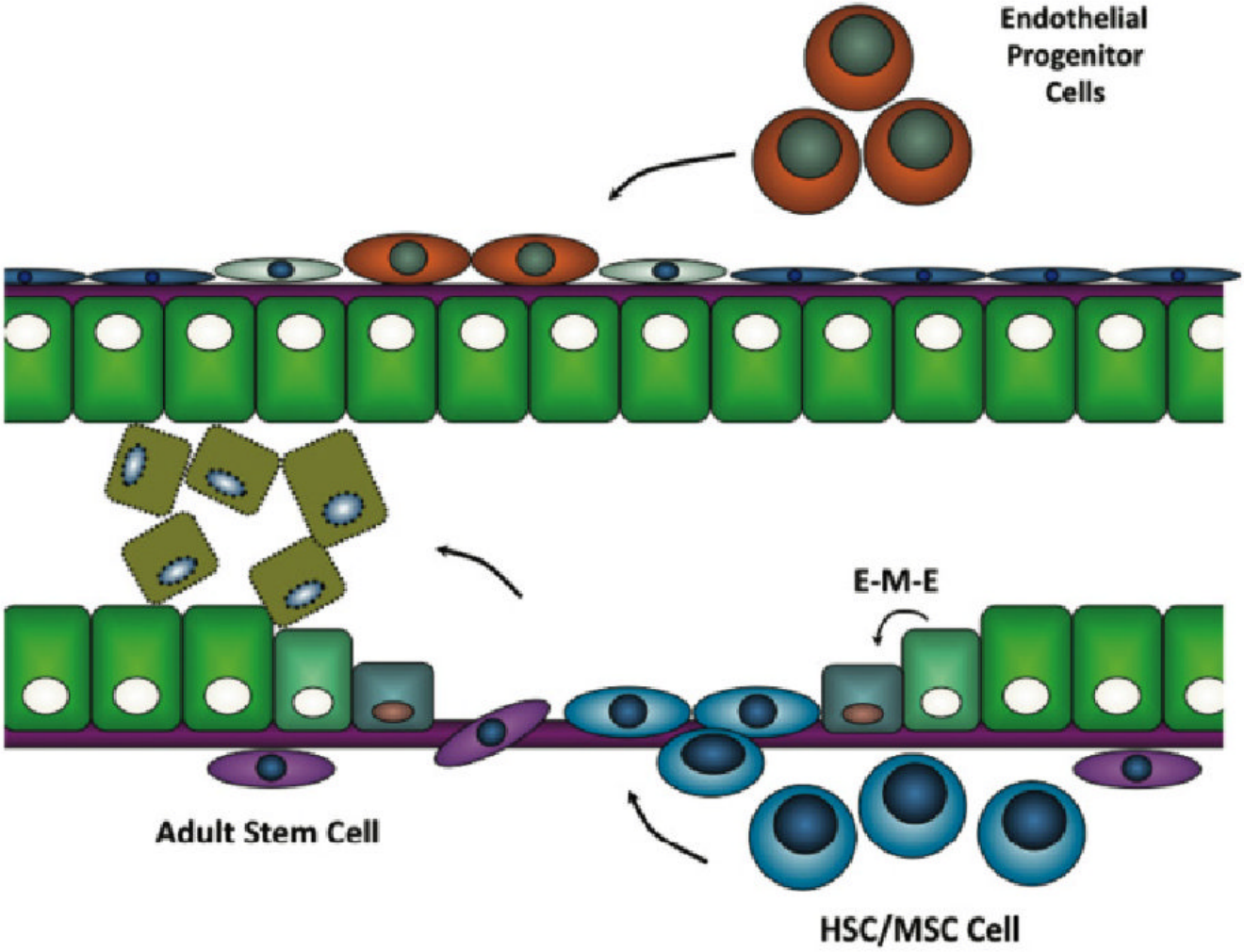

Fig. (1).

Progenitor cells in tissue repair following AKI. **A**) Adjacent surviving epithelial cells dedifferentiate undergo epithelial-mesenchymal-epithelial (EME) transition into new epithelial cells, **B**) kidney specific adult stem cells may migrate to the site of injury or **C**) bone marrow derived mesenchymal or hematopoietic stem cells gain access to the injured epithelium and differentiate into mature epithelial cells.