Review Article

Renal Ischemia-Reperfusion Injury Molecular Mechanisms and Therapeutic Targets

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Abstract
Ischemia/reperfusion injury (IRI) is caused by a rapid transient reduction in blood flow to a specific organ. IRI is typically accompanied by a strong inflammatory and oxidative stress response to hypoxia and reperfusion, which disrupts organ function. AKI caused by renal IRI contributes to a high morbidity and death rate in a variety of injuries. Although the pathophysiology of IRI is not fully understood, numerous key pathways leading to renal failure have been identified. The production of reactive oxygen species (ROS) during the reperfusion phase of the ischemic kidney and subsequent re-oxygenation begins a cascade of detrimental cellular reactions that leads to inflammation, cell death, and acute kidney failure. Greater knowledge of the cellular pathophysiological mechanisms causing kidney damage may lead to the development of more focused treatments to prevent and treat the damage. We discuss several significant possible mechanisms and treatment methods in renal IRI in this study.
Keywords: Ischemia/reperfusion injury, reactive oxygen species, oxidative stress response, hypoxia.

Ischemia/Reperfusion Injury in kidney

Ischemia/reperfusion injury (IRI) is defined as the restriction of blood supply to an organ followed by the restoration of blood flow and re-oxygenation. Injuries are unavoidable following infarction, infection, or organ transplantation. These processes aggravate tissue damage by triggering an inflammatory cascade that includes the activation of reactive oxygen species (ROS), cytokines, chemokines, and leukocytes[1, 2].

IRI contributes to the pathological condition known as acute kidney injury (AKI) in the kidney, which is a clinical disease characterized by accelerated renal failure and high mortality[3,4].

The pathophysiology of IRI in the kidney is highly complicated, although several pathogenic pathways are implicated, such as neutrophil activation, the production of reactive oxygen species, and other inflammatory mediators, such as adhesion molecules and a variety of cytokines.

The link between acute kidney injury and chronic kidney disease

A significant number of clinical epidemiological studies have provided a correlation between AKI and the development of chronic kidney disease (CKD)[5,6]. Despite the well-established epidemiological connection between AKI and CKD, evidence for a causal linkage between the two clinical entities remains elusive. Transplant recipients are a good cohort for studying the relationship between acute ischemia injury and the development of late organ failure. Ischemic damage in kidney transplantation first appears as delayed graft function (DGF), which is related to prolonged hospitalization and the requirement for renal replacement treatment after the donation.

Nonetheless, organ function is generally restored in DGF patients, showing some degree of acute ischemia damage resolution. Several investigations, however, have found that individuals with DGF are at a higher risk of acute rejection and have worse long-term renal function[7]. These data suggest a connection

between acute ischemia kidney damage and long-term graft function deterioration, despite relatively "normal" performance in the early phases. Several mechanisms for the development of chronic dysfunction have been postulated. It is critical to understand these processes as components of a complicated network with numerous overlapping, co-existing pathways, rather than as distinct pathophysiologic entities.

The renal response to hypoxia

Understanding the effect of ischemia on the kidney is dependent on understanding the anatomy of the nephron and renal microcirculation. Under normal conditions, the kidneys get around 20% of the cardiac output. This blood flow is largely directed to the cortex, with blood flow to the medulla coming primarily via the vasa recta, a continuation of the efferent arterioles of the juxtamedullary glomeruli. The kidney, particularly the outer medulla, performs at lower oxygen tensions than other regions of the body, both during normoxia and hypoxia[8]. Because of post-glomerular arteriovenous shunting and increased oxygen needs, this occurs when exposed to hypoxia, kidney blood flow can change drastically, particularly in the outer medullary area, decreasing oxygen supply and exacerbating hypoxic damage[9]. The ability of a kidney to resist an ischemic insult or to heal itself after an ischemia injury is largely reliant on nephron mass, pre-existing glomerulosclerosis, and arteriosclerosis[10]. The process by which a subsequent decrease in oxygen supply to the kidney causes AKI is well understood. However, establishing the involvement of hypoxia in the development of kidney damage over time is more difficult. Many studies have found a link between chronic tubulointerstitial hypoxia, oxidative stress, and chronic inflamemation, and that these factors are involved in the progression of CKD[11].

The role of inflammation and the immune system

IRI is a result of various mechanisms, including the host inflammatory/immune response. The initiation of inflammation occurs during ischemia, while post-ischemic events, such as ROS generation, amplifies the response. Therefore, the ischemic kidney is not merely the target of immune activation. Instead, it plays an active role in promoting immune activation. The acute inflammatory component of IRI involves the expression of cell surface adhesion molecules[12].

The longer duration of ischemia led to the loss of endothelial integrity and increased expression of vascular cell adhesion molecule (VCAM-1). Ischemic grafts also displayed enhanced and worse tubular necrosis[12].

The role of neutrophils and macrophages

The early and crucial component of neutrophil adherence to injured endothelial cells in the ischemic kidney is the initiation of damage. Interleukin 8 (IL-8), interleukin 10 (IL-10), RANTES, interleukin 17(IL-17), and monocyte chemoattractant protein-1 (MCP-I) have all been found to attract neutrophils to the transplanted organ within 6 hours after reperfusion[13-16]. Neutrophils will kill damaged cells by direct phagocytosis or degranulation, releasing proteases, myeloperoxidase, nitrogen species, antimicrobial peptides, and cytokines that contribute to the production of ROS[17]. Endothelial cell expression of ICAM1, E, and P selectin, which cross-talk with integrins and selectin on neutrophils, is also involved in neutrophil recruitment[16, 18, 19].

Inhibiting neutrophil accumulation in the kidney may help to avoid acute renal damage[13, 19, 20]. Other investigations, on the other hand, have failed to confirm the therapeutic benefits of neutrophil reduction, indicating a neutrophil independent mechanism in the pathophysiology of acute tubular damage[21, 22].

Nonetheless, the majority of data suggests that neutrophils play a role in the development of post-ischemic damage via mechanisms such as blockage of renal microvasculature and the production of free radicals and proteases[23]. Several studies have found a reduction in IRI severity following macrophage depletion before the injury[24], indicating a function for macrophages in promoting tubular damage during the early stages of IRI. Suppressing macrophage activity during the healing process, on the other hand, has been found to reduce tubular growth, affecting the normal recovery process.

As a result, macrophages' function in the renal response to IRI is complicated. Pre-clinical research has shown that macrophages have a role in the early inflammatory response, cellular

regeneration, tissue repair, and during the development of fibrosis. Depending on their activation and functional states, distinct subtypes of macrophages play these different roles.

Classical activation of macrophages typically involves interferon-gamma (IFNγ). Ischemia-induced cellular damage also results in the formation of danger-associated molecular patterns (DAMPs), which are detected by pattern recognition receptors (PRRs) and contribute to classical macrophage activation. These M1 macrophages that have been traditionally activated are pro-inflammatory and have been linked to tissue injury. They also, however, serve an important function in removing apoptotic cells and debris, which initiates the healing process[25].

M2a macrophages, which are crucial for wound healing, and M2b macrophages, also known as immunoregulatory macrophages, are examples of activated macrophages. M2a macrophages are activated by IL-4/IL-13 binding to the IL-4 receptor, which results in the release of growth factors, collagen precursor synthesis, and extracellular matrix generation. M2b macrophages control inflammatory responses by releasing immunosuppressive cytokines such as IL-10 and TGF-β. TGF-β production reduces inflamemation but may also contribute to the activation of pro-fibrotic pathways. When an injury persists, chemokines, macrophage colony-stimulating factors (M-CSF), and IL-34 are produced to keep macrophages recruited and retained[26].

Following experimental transplantation, blocking the M-CSF receptor exerts a protective effect[27]. Retention of M2b macrophages in damaged tissue results in the production of macrophage-derived factors, which then activate and support myofibroblasts, resulting in extracellular matrix deposition and fibrosis. The signals that keep pro-fibrotic macrophages in the kidney are yet unknown. Nonetheless, research utilizing the unilateral ureteral obstructive (UUO) rodent model suggests a function for the chemokine receptors CCR1, CCR2, and CX3CR1[26].

The role of the complement system

The complement system has already been recognized as an important early mediator of the post-ischemic inflammatory response[28,29]. The activation of complement is a critical component in the development of renal disease. Because complement plays a role in both the innate and adaptive immune responses to IRI, targeting it has shown to be an attractive therapeutic approach[30,31]. Ischemic kidney injury has been demonstrated to involve the anaphylatoxins C3a and C5a, which act via their respective receptors (C3aR and C5aR). C3a/ C5a receptors stimulation during IRI enhanced pro-inflammatory cytokine/chemokine production and tubular damage. The membrane attack complex C5b-9 has also been linked to the development of renal injury[32].

In response to ischemia, C-type lectin collectin-11 (CL-11/Colec11) was revealed to be an activator of the mannan-binding lectin (MBL) pathway in the kidney. CL-11 functions by detecting L-fucose in renal tubules after ischemia[33]. kidney-specific CL-11 deficiency decreases post-ischemic tubular damage and the functional loss, according to the findings.[33].

The role of natural killer cells, dendritic cells, and lymphocytes

Natural killer (NK) cells, renal dendritic cells (DCs), T cells, and B cells have been linked to early IRI, with their actions primarily involving direct targeting of injured tubular and endothelial cells, activation of neutrophils and macrophages, and secretion of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-4, and IL-10. If the function of NK cells is decreased, the degree of renal damage after IRI is also lowered[34-36]. TNF- α secretion by DCs contributes to post-ischemic kidney injury[37].

Initially thought to be bystanders, new data shows that T cells play an active role in the pathogenesis of IRI. CD4 and CD8 T cell depletion in murine IRI has been demonstrated to enhance renal function and decrease neutrophil infiltration and tubular atrophy[38].

Furthermore, in mice, inhibition of either αβ or γδ T-cells was linked with a reduction in renal damage[39]. Nonetheless, a subpopulation of T cells has been identified as being capable of preventing damage and promoting healing. It has been demonstrated that pre-and post-ischemia adoptive transfer of regulatory T cells protects the kidney from ischemic damage,

reduces TNF-α and IFN-γ production, and speeds up healing[40, 41].

The adaptive immunological response to IRI is mediated by B cells. Post-ischemic B cell activation has been demonstrated in investigations to be mainly harmful[42]. It has been demonstrated that depleting B cells in mice improves renal function and reduces tubular injury after ischemia[43]. Jang et al. discovered that B cell-deficient mice exposed to ischemia had more tubular proliferation, less tubular atrophy, and higher expression of IL-10 and VEGF[44].

Adoptive B cell transfer into these mice prevented this impact, indicating that B cells might interfere with post-ischemic healing mechanisms. In contrast, another research revealed that mice lacking all mature B cells had greater post-ischemic renal damage[45], indicating that B cells play a more complicated and diverse role in IRI development.

Tubular recovery

In the acute ischemic kidney, the proximal tubule is the primary site of damage. As a result, the degree and frequency of injury at this location play an important role in determining the reversibility of the damage and development to long-term organ failure. Severe and recurring injuries aggravate interstitial fibrosis, distal tubular damage, glomerulosclerosis, and tubular glomeruli[46].

Ischemic tubular damage is most visible in the S3 section of the proximal tubule and causes loss of cytoskeletal integrity at first[47]. The extent of cytoskeletal change is determined by the severity and duration of the ischemia. This loss of cytoskeletal integrity alters cellular polarity, cell-to-cell interactions, cell-to-matrix interactions, and function loss[48].

Tubular epithelial cells (TECs) have been demonstrated to actively participate in the development of post-ischemic tissue injury via a variety of methods. There is strong evidence that TECs produce pro-inflammatory and chemotactic cytokines in response to IRI[48-50], including TNF-α, IL-6, IL-1β, and TGF-β, as well as chemokines including MCP-1, IL-8, RANTES, and ENA-78[49].

This results in the recruitment of immune cells, which is required for the eventual repair of IRI and its damage. Damaged epithelial cells also create DAMPs, which serve as warning signals by activating a series of Toll-like receptors (TLR2, TLR3, and TLR4), as well as complement receptors and other co-stimulatory molecules that control T lymphocyte activity[51-53].

TLR-2 downregulation on kidney parenchymal cells has been demonstrated to lower the amount of pro-inflammatory cytokines (IL-1β, IL-6, MCP-1, and Keratinocyte Chemoattractant) generated by the kidney, giving functional and structural protection against IRI[52]. Wu et al., found that TLR4 was upregulated in TECs after IRI and that blocking TLR4 decreased the severity of IRI[53].

Furthermore, TLR4 knockout mice demonstrated less tubular damage and improved renal function preservation following IRI induction than wild-type mice[54].

Several investigations by Venkatachalam et al., also demonstrated that tubular cell arrest and atrophy are associated with increased production of fibrogenic peptides, which promotes interstitial pericytes/fibroblast proliferation via various routes, via the PI3K-Akt-mTOR, ERK-MAPK, JNK-MAPK, and TGF-β pathways[55-57], finally leading to nephron loss. Based on these findings, previous researches have looked at the use of cell cycle arrest biomarkers in the detection of AKI.[58].

Therapeutic approaches in ischemia-reperfusion injury

Myocardial hibernation, acute heart failure, brain dysfunction, gastrointestinal dysfunction, systemic inflammatory response syndrome, and multiple organ dysfunction syndromes have all been reported as clinical symptoms of ischemia-reperfusion damage. The therapeutic method varies depending on the damaged organ. In the case of sepsis, prompt resuscitation with sufficient fluids and vasopressors is essential[59-65].

Reperfusion arrhythmias are common problems in individuals having revascularization after acute myocardial infarction. To minimize ischemia-reperfusion damage and control malignant arrhythmias, staged gradual reflow or transient acid reperfusion are helpful treatment methods[66, 67].

The initial step in treating acute ischemic extremities injuries is to reduce ischemia

duration, rectify metabolic acidosis, and avoid acute kidney damage utilizing metabolic methods or anti-inflammatory therapies[68-70].

Nuclear transcription factors

NF-κB is a redox-sensitive transcription factor dimer composed of p50 and p65 that plays a crucial role in ischemia-reperfusion damage including a fast response to oxidative stress. Cell survival, apoptosis, and inflammation are all regulated by NF-κB activation via effectors such as Manganese superoxide dismutase (MnSOD), Bcl-2, TNF-, intercellular adhesion molecule-1 (ICAM), and P-selectin. NF-κB is inactive in normal Kupffer cells, and its complexes prevent the production of protein I-κB. NF-κB is activated in several ways after ischemia-reperfusion injury: the traditional pathway, in which IκB is phosphorylated by its kinase complex, followed by degradation; without the IKK complex (IκB kinase) pathway, IκBa tyrosine residues are phosphorylated, and NF-κB is activated.

When NF-κB is activated, it is transported to the nucleus and activates the target gene for transcription, contributing to ischemia-reperfusion damage. NOS, cytokines (TNF-α, IL-1β), chemokines (ENA78), and ICAM-1 are all regulated by NF-κB. In animal studies, NF-κB activation was linked to ischemia-reperfusion damage, and administration of NF-κB inhibitors decreased IRI [71].

Conclusion

Renal damage caused by ischemia/reperfusion is the result of a dynamic process combining inflammation and several mediators in a complicated interaction. Oxidative stress and lipid peroxidation appear to be important variables that enhance the inflammatory process during IRI. A deeper knowledge of pathophysiology and treatment methods underlying the functional abnormalities observed in ischemic acute renal failure would also necessitate consideration of the illness's complexity.

Conflicts of interest

The authors declared no competing interests.

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