Mechanisms of Inflammation and Oxidative Stress in Acute Kidney Injury

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Abstract : Acute kidney injury (AKI) is a sudden decline in kidney function. AKI is at risk of progressing end-stage renal disease requiring hemodialysis. Increasing evidence suggests inflammation and oxidative stress important role in the pathogenesis of AKI. The purpose of this literature review is to investigate the role of inflammation and oxidative stress in AKI. Methods were conducted following the literature review guidelines. Inclusion criteria were reference sources less than 5 years old and data related to inflammation and oxidative stress in AKI. Exclusion criteria were manuscripts that were not fully accessible and unverified sources. AKI is commonly caused by reduced renal blood flow, structural damage to the kidney, and inflammation / obstruction. Cellular damage and molecular products are the main triggers of inflammation and the resulting ROS. Reperfusion increases ROS that activate various pathways causing cell membrane, cytoskeleton and DNA injury. The adaptive response after AKI is the repair of renal function and structure, but maladaptive responses can occur by inflammatory persistence, fibroblast proliferation and excessive extracellular matrix deposition. AKI involves complex interactions between the renal parenchyma and the immune system resulting in inflammation, apoptosis and oxidative stress leading to impaired renal function.

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INTRODUCTION

Acute kidney injury (AKI) is defined by a sudden reduction in kidney function, complicated by immune system and renal parenchyma interactions that cause inflammation at the location of damaged kidney tissue and compromised kidney function. AKI significantly increases the risk of end-stage renal disease and chronic kidney disease (CKD). Depending on the location of care and the parameters used to define AKI, the incidence differs between nations. 10% to 15% of hospitalized patients have AKI, and this percentage rises to 50% in patients admitted to intensive care units.(Turgut et al., 2023).

The etiology of AKI multifactorial and associated with complex pathophysiologic mechanisms with different types of damage. AKI is commonly caused by renal ischemia reperfusion damage (IRI). IRI renal causes loss of tubular epithelial cell brush border and impaired cell polarization leading to tubular obstruction, cell necrosis and apoptosis (Deng et al., 2020).

The pathological processes associated with ischemia and the reperfusion (restoration of blood flow) are linked to the activation of several pathways that may be targets for lessening the severity of renal injury. The aseptic inflammatory process, which involves innate and adaptive immunology as well as oxidative stress pathways that mostly occur during the reperfusion phase and ultimately cause organ damage and macromolecular damage as well as cell death, is one of the key routes of GGA.(Andrianova et al., 2020).

The etiology and pathogenesis of AKI are underpinned by a complex network of disease processes, including autophagy, inflammation, apoptosis, necrosis, endoplasmic reticulum stress, reactive oxygen species (ROS/Reactive Oxygen Species), and mitochondrial dysfunction. Understanding the mechanisms of inflammation and oxidative stress involved in AKI is one way to identify early targets for treatment, prevention or early markers of AKI. This paper aims to investigate the role of inflammation and oxidative stress in AKI

METHODS

This literature study was conducted following the literature review guidelines. Inclusion criteria were reference sources less than 5 years old presenting complete reviews and data related to inflammation and oxidative stress in AKI. Exclusion criteria were manuscripts that were not fully accessible and unverified sources.

RESULTS AND DISCUSSION

There are four stages in which ischemic AKI can occur: initiation, extension, maintenance, and recovery.The initiation phase is caused by decreased blood flow to the kidneys causing microvascular damage characterized by cytological changes in tubular epithelial cells, obstruction, inflammation and coagulopathy. This phase initiates the generation of cytokines and chemokines in response to acute injury and initiates the inflammatory cascade pathway. When hypoxia continues and ischemia and inflammatory responses within 24 hours stimulate the extension phase, vascular cell damage and apoptosis and necrosis of renal tubular epithelial cells begin to occur.The body attempts to stop this extension phase process by producing anti- inflammatory ,this phase is called the maintenance phase, where cellular changes are repaired and inflammation is reduced. The recovery phase is characterized by vascular and renal epithelial cells regaining their original structure and function.

1. Inflammatory Process in AKI

1.1 Endothelial and renal tubular cells

The kidney has a very high energy demand and a relatively low oxygen partial pressure, with values ranging from 10–20 mmHg in the renal medulla to 40–60 mmHg in the cortex. As a result, the renal vascular architecture is very susceptible to oxygenation and blood perfusion. Reduced glomerular filtration rate (GFR), a defining feature of acute kidney injury (AKI), poor renal perfusion, persistent renal hypoxia, and epithelial cell damage can all result from altered endothelial function during renal ischemia.

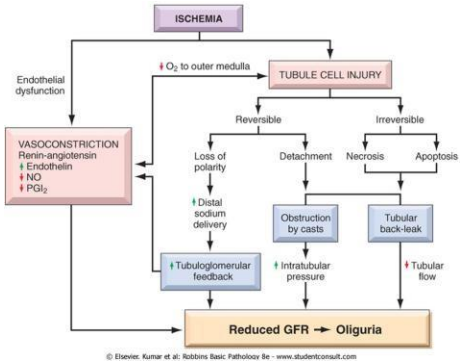

Figure 1. Ischemic injury in the initiation phase of GGA causes sublethal endothelial injury-mediated vasoconstriction, leading to endothelial vasoconstrictor endothelin release and decreased nitrate production for vasodilation and there is evidence of a direct effect of ischemia on the glomerulus causing reduced LFG (glomerular filtration rate).

1.2 Apoptosis and necrosis in GGA

In the kidneys of humans, mice, and rats, renal ischemia reperfusion damage significantly alters the Bax/Bcl-2 ratio in the pro-apoptotic direction, increasing Bax and decreasing Bcl-2. Using Bax or Bak-deleted animals, several researchers revealed the significant roles of Bax and Bak in tubular cell death in ischemia-type AKI. These mice were protected from ischemic AKI by global Bak removal or proximal tubule-specific Bax deletion. (Han & Thomas Lee, 2019).

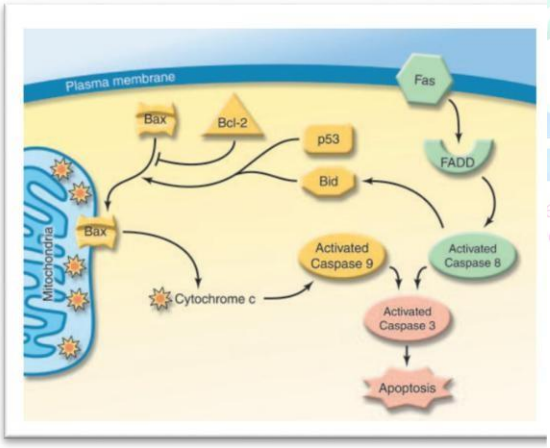

Figure 1. The extrinsic pathway requires plasma membrane Fas receptor activation, with signal transduction through FADD resulting in caspase 8 activation. Translocation of Bax to the mitochondria is necessary for the intrinsic route because it creates holes that allow cytochrome c to be released and caspase 9 to be activated. By activating Bid, cross communication between these routes is made possible. Additionally, the p53-dependent pathway activates Bax. Normal cells are protected against Bax activation by Bcl-2 and Bcl-xL. The last morphologic cascade of apoptosis is started by caspase 3, which is activated by both caspases 8 and 9. Significant therapeutic promise is offered for acute renal failure in humans when this route is inhibited.

Many factors can cause renal ischemia injury to tubular epithelium, including loss of epithelial brush boundary and cell polarity, cell death, survival cell differentiation, proliferation, and normal epithelium restoration. as shown in Figure 2 above. The cytoskeleton of tubule epithelial cells has important functions including maintaining polarity, endocytosis, signal transduction, motility, organelle movement, exocytosis, cell division, and membrane protein adhesion. Tubular epithelial cells after experiencing ischemia have less severe injury so that they can recover both functionally and structurally, while cells that experience severe injury experience apoptosis or necrosis which causes cell death (García-Ortuño & Bobadilla, 2018).

1.3 Cytokines and chemokines in GGA

Leukocytes and renal tubular cells produce a large number of cytokines into the injured kidney during the initiation and extension phases of acute kidney injury(AKI).Proinflammatory cytokines/chemokines IFN γ, IL-2, IL-10, GM-CSF, TGF-β, CXCL1, IL-6, MIP-2, and MCP-1 are elevated in the kidney in ischemic AKI. IL-18 is a proinflammatory cytokine produced by renal tubular proximal cells, lymphocytes, netrophils and macrophages. Several studies on ischemic reperfusion injury model rats have shown that IL-18 increases significantly after ischemic injury. Rat models with higher levels of IL-18 were found to be protected from ischemic reperfusion injury and showed better renal function, less tubular damage and infiltration of neutrophils or macrophages. IL-18 inhibitor treatment showed a protective effect against kidney damage, also reducing the number of profibrotic molecules in the kidneys of AKI rat models of ischemic reperfusion injury. IL-18 is activated by caspase-1 so that inhibition of caspase 1 is beneficial to protect AKI induced ischemic reperfusion injury (Hirooka & Nozaki, 2021).

Proinflammatory cytokines including Tumor necrosis factor alpha (TNF α) and IL-6 generated by injured tubular epithelial cells or from T lymphocytes are implicated as major contributors to reperfusion ischemia-induced kidney injury. TNF-α

is mainly expressed by renal tubular cells, macrophages, mesangial cells and plays a role in cell damage, enhancing inflammatory processes and death signaling pathways, including cell death receptors and caspases that mediate cell death. TNF-α is also elevated during the healing phase and has the effect of overcoming inflammation through TNFR2. The proposed mechanism is that TNF-α activates NF-κB, promoting cell survival. TNF, IL- 1, and IL-6 mediate protective systemic effects of inflammation, including fever, acute phase protein synthesis by the liver, and increased leukocyte production by the bone marrow (Black et al., 2019).

1.4 Neutrophils and inflammatory AKI

One of the main causes of renal injury is neutrophil accumulation in the kidney following ischemia injury in animal models and acute kidney injury (AKI) in humans. Neutrophils cling to endothelial cells via particular adhesion molecules (P-selectin and intercellular adhesion molecule-1) and, in conjunction with platelets and erythrocytes, also restrict capillaries, resulting in vascular blockage. Neutrophil degranulation; In the outer medulla, endothelial and epithelial cells can sustain damage and be aggravated by the release of proteases, myeloperoxidase, and cytokines, as well as the creation of reactive chemicals. ROS, proteinases, elastase, myeloperoxidase, and cationic peptides are released following reperfusion. In addition to other inflammatory leukocytes like natural killer cells, monocytes, and macrophages, neutrophils also recruit and activate other inflammatory leukocytes through the release of proinflammatory cytokines and chemokines. These leukocytes work in concert to cause renal injury.(Bolisetty & Agarwal, 2009; Han & Thomas Lee, 2019).

Enzymes produced by neutrophils break down the extracellular matrix. Fibrosis may worsen if neutrophil recruitment persists after the acute period due to tissue injury. In a study using a rat model of unilateral ischemic reperfusion injury AKI leading to chronic renal failure, neutrophil counts were found to be elevated for up to 2 weeks, and these rats showed marked interstitial fibrosis. Combined, these findings imply that modifying neutrophils in renal damage can significantly alter the course of the disease since lowering neutrophil levels or preventing neutrophil accumulation can avoid AKI. In vivo during the acute tubular necrosis phase, neutrophils, can rapidly infiltrate and play a role in renal fibrosis (Black et al., 2019; Wang & Zhang, 2022).

1.5 Macrophages and GGA inflammation

During the initial phase of ischemia reperfusion injury in the kidney, macrophages are crucial to the immune response. Macrophages are classified as either M1 or M2 kinds depending on how they are activated. The M1 type is typically activated by the NF-κB route, whereas the M2 type is alternatively activated by the JAK/STAT, MAPK, PI3K, and other pathways. In addition to secreting proinflammatory chemokines and cytokines and presenting antigens throughout the immune response, M1 macrophages are capable of generating an acute inflammatory response. In contrast, M2 macrophages facilitate wound healing, angiogenesis, and inflammation resolution. (Chen et al., 2022).

Rodent model of ischemic GGA, macrophage infiltration began to increase at 1 hour of injury, reached a peak within 24 hours and remained for more than 7 days. Infiltration and activation of M1 macrophages after the kidney undergoes ischemic reperfusion injury produces many reactive oxygen species (ROS), nitrogen intermediates and proinflammatory cytokines, such as TNF α and IL-1β, which can boost the Th1 immune response and activate additional leukocytes. In cases of severe or recurrent kidney injury, M2 macrophages can also release a number of profibrotic growth factors, including transforming growth factor-b1 (TGF-b1) and epidermal growth factor (EGF), which can activate interstitial fibroblasts and build intracellular matrix. The damaged tubular cells emit chemokines that stimulate the kidney's M2 macrophage invasion through the use of integrins, selectins, and trans-endothelial migration. They also continuously generate growth factors and cytokines. Following AKI, M1 and M2 macrophages in the kidney exhibit distinct activities. (Chen et al., 2022).

1.6 Dendritic cells, Toll-like receptor (TLR)

In the interstitium of normal rat kidneys, dendritic cells expressing CD11c and MHC class II are prevalent and play a crucial role in mediating the interaction between innate immunity and adaptive immunity. Because they release proinflammatory cytokines and chemokines, dendritic cells are the primary initiators and potentiators of the innate immune system. Natural killer T (NKT) cells will

interact with substances including TNF, IL-6, MCP-1, and RANTES, which will contribute to reperfusion ischemic kidney injury. (Han & Thomas Lee, 2019). Toll-like receptors (TLRs) are transmembrane receptors that have been conserved throughout evolution and are the archetypal pattern recognition receptors (PRRs). TLR-triggered signal transduction phosphorylates NF-κB and numerous kinases, which in turn activate innate immune system effector cells and produce pro-inflammatory cytokines. Beginning with TLRs, signal transduction triggers the innate immune system's effector cells by activating NF-κB and numerous kinases, which in turn generate pro-inflammatory cytokines. The activation of sterile (non-microbial) innate immune receptors, such as TLR (Toll like receptor) and NLR (Nod like receptor), is one of the first steps in the development of ischemic-induced AKI. Proinflammatory cytokines and chemokines are secreted as a result of these receptors' activation, which also activates several other intracellular pathways like NF-κB, mitogen-activated protein kinase (MAPK), and c- Jun N-terminal kinases (JNK) (Vallés et al., 2023). During reperfusion ischemic injury, sterile inflammation is caused by the production of Toll- like receptors-2 and -4 (TLR-2 and TLR-4) by the kidney. When TLRs are activated, proinflammatory mediators such TNF-α, MCP-1, IL-8, IL-6, IL-1β, and TGF-β are upregulated. (Arfian et al., 2019).

2. Oxidative Stress Mechanism In AKI

2.1 Source of ROS

The breakdown of ATP into ADP and AMP occurs quickly in renal ischemia. AMP is further broken down into adenine nucleotides and hypoxanthine as a result of extended ischemia. The accumulation of hypoxanthine contributes to the formation of reactive oxygen molecules, adenine nucleotides diffuse freely out of the cell, and their depletion hinders intracellular ATP re-synthesis during reperfusion. There is currently strong evidence regarding the role of reactive oxygen species in the pathogenesis of GGA. Superoxide and hydrogen peroxide are produced during reperfusion when accumulated hypoxanthine is converted to xanthine (catalyzed by xanthine oxidase, which is created from xanthine dehydrogenase, either as a result of proteolytic conversion or as a result of oxidation of sulfhydryl residues). Iron and hydrogen peroxide form highly reactive hydroxyl radicals in the kidney. At the same time, In tubule cells, ischemia activates NO synthase. The produced NO then combines with superoxide to form peroxynitrate, which causes nitrosylation of proteins and oxidative damage to cells. Reactive oxygen species damage renal tubular cells by inducing apoptosis, damaging DNA, oxidizing proteins, and lipid peroxiding together. (Gyurászová et al., 2020).

Hydrogen peroxide (H2O2), superoxide anion radical (O2-), and hydroxyl radical (HO) are produced when cytochrome oxidase reduces oxygen in the mitochondrial electron transport chain. This is the primary source of ROS creation. There is no specific damage target for ROS, However, assaults on proteins, lipids, and amino acids lead to the creation of unstable molecules, which function as radicals before changing into substances with diverse metabolic consequences. Lipid, protein, and nucleic acid peroxides are thus members of the ROS family. Xanthine oxidase, adrenaline/epinephrine, and NADPH oxidase complex (Nox) are minor ROS generators (approximately 10% total). ROS-induced pathways include lipid peroxidation, cellular death, and imbalanced calcium concentration (Wu et al., 2018).

CONCLUSIONS

. Acute renal failure involves complex interactions between the renal parenchyma and the immune system giving rise to inflammatory processes, apoptosis, and oxidative stress at the site of renal tissue causing impaired renal function

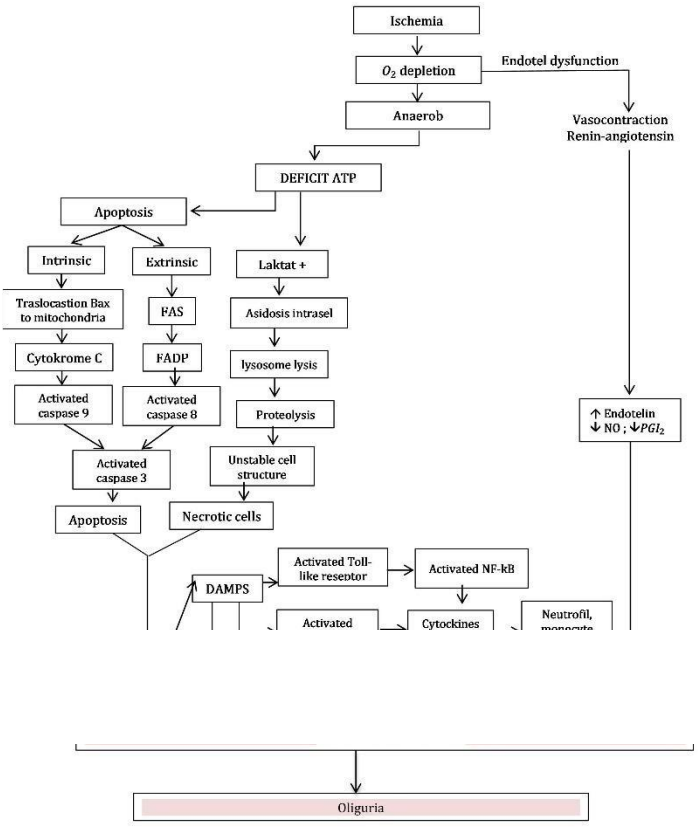

Figure 2: Inflammatory pathways in GGA that causes cell necrosis and apoptosis leading to impaired renal filtration function. ATP: Adenosin triphosphate; iNos: Inducible nitric oxide synthase; NO: Nitric oxide; ROS: Reactive Oxygen Species.

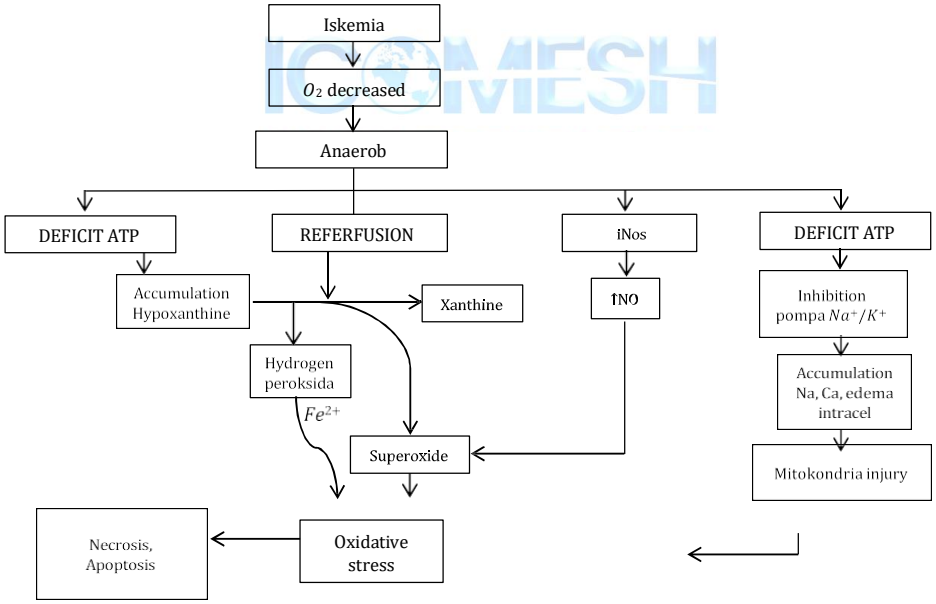

Figure 3: Inflammatory pathways leading to renal tubular cell damage cause a decrease in glomerular filtration rate GGA. ATP: Adenosin triphosphate; FAS: Fatty acid synthase ; FADP: ;NFκB: Nuclear factor-κB; NO: Nitric oxide; PGI_2: Prostaglandin I2 (Prostacyclin); DAMPs: *damage-associated molecular patterns:*

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