NEUTROPHILS—A KEY COMPONENT OF ISCHEMIA-REPERFUSION INJURY

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ABSTRACT—Ischemia-reperfusion injury (IRI) is a common occurrence following myocardial infarction, transplantation, stroke, and trauma that can lead to multiple organ failure, which remains the foremost cause of death in critically ill patients. Current therapeutic strategies for IRI are mainly palliative, and there is an urgent requirement for a therapeutic that could prevent or reverse tissue damage caused by IRI. Neutrophils are the primary responders following ischemia and reperfusion and represent important components in the protracted inflammatory response and severity associated with IRI. Experimental studies demonstrate neutrophil infiltration at the site of ischemia and show that inducing neutropenia can protect organs from IRI. In this review, we highlight the mechanisms involved in neutrophil recruitment, activation, and adherence and how this contributes to disease severity in IRI. Inhibiting neutrophil mobilization, tissue recruitment, and ultimately neutrophil-associated activation of local and systemic inflammatory responses may have therapeutic potential in the amelioration of local and remote tissue damage following IRI.

KEYWORDS—Inflammation, multiple organ failure, migration, cytokines

ISCHEMIA-REPERFUSION

Clinical setting of ischemia-reperfusion

Ischemia-reperfusion (IR) has been recognized as a cause of clinical sequelae for more than half a century (6) and remains a common occurrence in coronary bypass surgery, organ transplantation, gut hypoperfusion, and stroke (7, 8). IR is recognized as a complex cascade of events including interactions between vascular endothelium, interstitial compartments, circulating cells, and numerous biochemical entities that follow ischemia. Inflammation is a key mediator of IR, and aspects of the involvement of the innate immune system have been reviewed by others (8–10). Despite our knowledge of the pathophysiology of IR, injury caused by IR precedes clinical observation, and once apparent, it is often too late for intervention. Hence, there is still a need for a therapeutic that could prevent or reverse the effects of the injuries caused by IR (7). A number of failed clinical trials demonstrated that intervention during the first seconds of reperfusion is imperative, and thus the window of opportunity during reperfusion is limited. Therefore, therapeutic options need to be fast acting, readily available by clinicians, and not adversely damaging in their own right.

Causes and effects of ischemia-reperfusion injury

IR is initiated by an ischemic episode, where blood supply is restricted to a portion of an organ or the whole organ, initiating cell death, which is further exacerbated when blood flow is returned. Ischemia results in tissue hypoxia that causes a build-up of metabolic intermediates and reactive oxygen species (ROS), namely, superoxide, hydrogen peroxide, and hydroxyl radicals. Reactive oxygen species increase intracellular calcium, cause pH changes, and concomitantly deplete ATP and nitric oxide (NO), resulting in damage to cell organelles and leading to necrotic cell death (2, 7). Excessive periods of ischemia, ranging from a few minutes to half an hour or more (11–13), depending on the organ, activates metabolic intermediates and ROS resulting in an overwhelming inflammatory response that leads to ischemia-reperfusion injury (IRI). Increased ROS quenches the production of NO and damages endothelial cells, resulting in loss of barrier integrity and release of ROS into the extracellular matrix (13, 14). This increases expression of adhesion molecules (8); acts as a chemoattractant for neutrophils, initiating their recruitment (14); activates the complement cascade (15, 16); and promotes apoptotic cell death (17, 18). Resident macrophages and damaged endothelial cells release proinflammatory cytokines, further recruiting, activating, and aiding in migration of neutrophils. This overwhelming inflammatory response can lead to acute respiratory distress syndrome (ARDS) or systemic inflammatory response syndrome (SIRS) that are central to the pathogenesis of multiple organ failure (MOF) (1–4), which has a mortality rate of 70% (5). IR injury physiology is complex, but the primary response cells to IRI are neutrophils, which infiltrate the damaged tissue within minutes of activation. Several studies in the 1980s and 1990s investigated the role of neutrophils in IRI (19). In the past 2 decades, more emphasis has been given to the role of molecular, rather than cellular, targets such as...
complement receptors (20), Toll-like receptors (TLRs) (21), ROS (20), and the proinflammatory cytokines such as tumor necrosis factor α (TNF-α) (that was subsequently shown not to be involved in IRI) (22). The roles of cytokines, ROS, complement, and TLRs have been emphasized in the pathogenesis of IRI (20, 21) and support, activate, recruit, and amplify the destructive function of neutrophils. Nevertheless, recent studies have returned focus to the role of neutrophils as a key player in the pathophysiology of IRI (20, 21) and support, activate, recruit, and amplify the destructive function of neutrophils. Nevertheless, recent studies have returned focus to the role of neutrophils as a key player in the pathophysiology of IRI (16, 23–25). In this review, we highlight the feedback loop of neutrophil recruitment and excessive damage at the site of IRI and how this can result in MOF.

**Neutrophils in IRI**

At the site of IRI, activated neutrophils further exacerbate host tissue damage through release of ROS, proteinases, and cationic peptides (26). Neutrophils produce a large quantity of ROS when nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is activated upon adhesion or by proinflammatory cytokines (27). Neutrophils block capillaries preventing reperfusion of the tissue, which leads to tissue necrosis and an exacerbated immune response. Neutrophils secrete proinflammatory cytokines and chemokines to create a positive feedback loop of neutrophil recruitment and activation (16, 28), as illustrated in Figure 1. Furthermore, neutrophil migration causes loss of epithelial barrier integrity and downregulation of junctional adhesion molecule-C (JAMC). JAMC prevents reverse migration of neutrophils (29), which is associated with ARDS, SIRS, and MOF (1, 22, 26).

IR can affect every part of the body and is initiated by various mechanisms, depending on the organ or area involved. Therefore, the overactive state of neutrophils in response to excessive ROS, which is also present in normal tissues at lower levels, rather than activation induced via cytokine signaling, could be one reason why a therapeutic to treat or prevent IRI remains elusive. Given the complex pathology of IRI, it is instructive to examine the role of neutrophils in specific organs, the mechanisms involved in IRI in that organ, and how neutrophils contribute to disease severity regardless of the mechanisms involved in recruiting and activating them.

**NEUTROPHILS IN ORGAN-SPECIFIC IRI**

**Heart**

Cardiac IRI is common after coronary bypass surgery, with myocardial infarction being the leading cause of mortality and morbidity in adults in developed and developing nations (30). After prolonged ischemia, restoration of blood flow induces ROS and production of TNF-α, interleukin 1 (IL-1), IL-6, IL-8, peptide-activating factor (PAF), and macrophage inflammatory factor 2 by endothelial cells, mast cells, and myocytes (31). It also activates complement initiating production of C5a (20). These events significantly increase neutrophil infiltration at the site of IRI, which directly correlates to infarct size (31). Adhesion molecules, such as CD11, CD18, P-selectin, and intercellular adhesion molecule 1 (ICAM-1) on the endothelium are also

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**Fig. 1. Positive feedback loop of cytokine release and neutrophil recruitment.** Ischemic tissue and resident macrophages at the site of ischemia release ROS and cytokines. ROS activates complement and drives chemotaxis of neutrophils into the ischemic tissue, along with IL-1 and C5a, which initiate rapid neutrophilia. Complement proteins and cytokines bind to activated neutrophils at the site of ischemia. This promotes production of further proinflammatory cytokines and upregulates expression of adhesion molecules. C5a binds to the C5a receptor (C5aR) on neutrophils and stimulates NF-κB, which initiates transcription of TNF-α, IL-8, and IL-6. TNF-α promotes production of IL-1 and upregulates expression of CD11/CD18 integrins, which are required for firm adhesion to the epithelial/endothelial cell, enabling migration across the endothelial/epithelial barrier. IL-6 promotes neutrophilia, and IL-6 stimulates granulopoiesis in the bone marrow. This overwhelming response of neutrophil infiltration and cytokine production overrides protective mechanisms, leading to a positive feedback loop of neutrophil mobilization, production, recruitment, migration, and subsequently excessive damage beyond that of the initial insult.
upregulated, which then activates neutrophils and enables migration through the endothelium. Neutrophils have deleterious effects in three ways. First, they release a large amount of ROS, which exacerbates tissue damage (14). This was verified in a canine model by electron paramagnetic resonance spectroscopy that showed neutrophils as the major source of ROS during reperfusion (32). Second, they contribute to the no-reflow phenomenon. This can expand the ischemic insult to more than 50% of the capillaries exacerbating tissue damage and necrosis and thus upregulating proinflammatory signals, adhesion molecules, and neutrophil infiltration (31, 33), through the neutrophil feedback loop (Fig. 1). Finally, enthusiastic migration of neutrophils across the endothelial barrier leads to tight junction loss (31, 34) and potentially MOF.

Various animal models inducing neutropenia in feline, canine, bovine, and rodents have exhibited reduced tissue necrosis and myocardial injury (35, 36), as well as demonstrating preservation of endothelial function (37). Chandrasekar and colleagues (39) investigated the role of the proinflammatory cytokines IL-6, IL-1β, and TNF-α, demonstrating that neutrophil depletion in rats significantly inhibited expression of these cytokines independently of nuclear factor κB (NF-κB) (38). Knockout models of P-selectin (40) and ICAM-1 (40, 41) further corroborate the damaging role of neutrophils in IRI as myocardial necrosis in mice was attenuated in relation with reduced neutrophil infiltration.

**Kidney**

IRI is a major cause of acute kidney injury, which has a mortality rate in critically ill patients around 50% and causes significant comorbidity (8, 42, 43). Neutrophil infiltration in kidney IRI is seen as early as 30 min after reperfusion and is evident in both animal models and patient biopsies (25). Awad and colleagues (43) recently carried out an extensive study on the role of neutrophils in kidney IRI in a murine model that clamps the renal pedicles to induce IRI. They showed that neutrophil transmigration into the interstitial compartment is responsible for vascular permeability and damage in the kidney.

IRI causes injury to tubular epithelial cells, endothelial cells, and dendritic cells. Resident dendritic cells produce TNF-α, IL-6, monocytic chemotactic protein 1 (MCP-1), RANTES (regulated on activation, normal T cell expressed and secreted) (44), macrophage inflammatory protein 2 (MIP-2), and keratinocyte-derived chemokine (the mouse analog of human IL-8) (42), initiating a potent chemotactic gradient for neutrophil recruitment. Interestingly, in the kidney, IL-8 plays a crucial role in neutrophil recruitment and mediates tissue injury via cytokines, free radical intermediates, and proteases (42, 44). Increased expression of ICAM-1, P-selectin, and IL-8 (45), enables increased adhesion, which has been attributed to nephron destruction (46). Upon degranulation, neutrophils release proteases, myeloperoxidase (MPO), cytokines, and generation of ROS in the outer medulla (42), broadening tissue damage throughout the kidney. Furthermore, neutrophils in conjunction with platelets and red blood cells cause blockage to the capillary, resulting in the no-reflow phenomenon (25), which amplifies the inflammatory response and thus neutrophil infiltration. Activation of the complement system, specifically C3, C5a, and membrane attack complex (C5b-9), is also seen in kidney IRI (42, 47). Membrane attack complex deposition stimulates TNF-α and IL-6 and downregulates Crry, a complement inhibitor on the tubular epithelium (42).

**Lung**

Lung IRI can be initiated by several conditions including lung transplantation, cardiopulmonary disease, trauma, resuscitation, atherosclerosis, and pulmonary embolism and remains a significant cause of morbidity and mortality (48). Lung IRI can also be initiated from ischemic insult in other organs such as the intestine. Lung injury after intestinal IRI is characterized by increased microvascular permeability, alveolar capillary endothelial cell injury, reduced lung tissue ATP levels, and neutrophil infiltration (49).

Production of ROS is immediately induced upon reperfusion, primarily from alveolar macrophages and endothelial cells. NF-κB, NADPH oxidase, inducible NO synthase, and the proinflammatory cytokines IL-8, IL-12, IL-18, TNF-α, and PAF are activated. These amplify the expression of ICAM-1, CD18, and P-selectin on the endothelial side of the lung (48). These events begin to impair lung function and recruit neutrophils, which generate additional ROS, IL-8, PAF, TNF-α, and MPO. Neutrophils are particularly damaging during this phase as they increase lung permeability and facilitate tissue damage (50). Neutrophilia induced in a rat model provides protection from tissue damage corroborating that neutrophils are key in the severity of tissue damage (51). Although IL-8 correlates directly to mortality rate after lung transplantation (48), it predominantly induces chemotaxis in neutrophils (52); indicating that higher mortality rates are most likely due to the damage caused by infiltrating neutrophils rather than IL-8 itself.

**Liver**

The role of neutrophils in liver IRI was well defined by Jaeschke and colleagues (53) in the early 1990s and showed that neutrophils exacerbate liver damage. More recently, reviews by Ramaiah and Jaeschke (24) and Kubes and Mehal (54) provide compelling evidence for the role of neutrophils in liver IRI. MIP-2 and keratinocyte chemoattractant are the main chemoattractants in the liver, which along with TNF-α, IL-1β, and IL-8 promote neutrophil accumulation and expression of the CD11/CD18 integrin (24). In the liver, neutrophils adhere within sinusoids independently of selectins, eliminating the requirement of rolling (54). However, activation and accumulation of neutrophils in the sinusoids do not cause tissue damage to the epithelium, as it does in other organs. Only after migrating across the endothelium and in close proximity to the hepatocytes can neutrophils cause damage by oxidative stress, triggered through interaction with CD11/CD18 integrins, NADPH oxidase, and MPO (24, 55). Transendothelial neutrophil migration therefore is an important step in liver IRI, which is controlled by expression of CD11/CD18 and the subsequent binding to ICAM-1 (56, 57). This was further corroborated by Jaeschke and Woolbright (55) in 2012, when they identified the role of complement in directly priming neutrophils for ROS formation and activation of CD11b expression. They also showed that complement promotes Kupffer cell–induced oxidant stress and injury, which indirectly enhances neutrophil responses (55). The role of neutrophils in liver IRI is further supported through the
protective effects seen in animal models of neutropenia (58, 59). Although neutropenia is protective, inducing neutropenia in clinical patients would severely immunocompromise them, making them susceptible to many pathogenic diseases. This is why we need to focus on modulating neutrophil behavior rather than preventing it completely.

**Gut**

Intestinal IRI has a relatively small incidence rate, with only 30,000 cases reported per annum in the United States, and has therefore not been given as much attention as other organs. However, intestinal IR is often a secondary event to most critical conditions (60), with severe secondary events being associated with atherosclerosis, obesity, diabetes (16, 61), and α-adrenergic agents or digitalics (3).

Recent evidence reveals neutrophils are a key player in the pathophysiology of intestinal IRI (16, 23, 62), and our histological staining of mouse ileum illustrates neutrophil infiltration and villi destruction (Fig. 2). Importantly, neutrophil depletion has shown to protect the intestine from late-stage mucosal damage and afford protection to remote organs (63–66).

The initial insult, as is characteristic with IRI in all organs, is from ROS. ROS themselves are key mediators in intestinal IRI; they are a primary source of damage initially compromising the integrity of the endothelial barrier (11, 13, 67), promote activation of complement, attract neutrophils, and enhance expression of cell adhesion markers increasing extravascular migration to the sites of inflammation resulting in vascular injury (16, 28, 68).

Complement is activated independently through ROS and neutrophil activation and leads to the production of C5a and IL-1β, potent chemoattractants for neutrophils. C5a further stimulates NF-kB upregulating transcription of proinflammatory cytokines recruiting more neutrophils (11, 69). C5a receptor (C5aR) knock-out models show reduced intestinal mucosal damage and decreased neutrophil infiltration, attenuate neutrophil apoptosis, and prevent cytokine release into the plasma (70). TLR-2 and TLR4 contribute to the initiation of an inflammatory response (9) as they signal macrophages, monocytes, and dendritic cells to further recruit neutrophils through production of cytokines.

**Neutrophils and MOF**

In intensive care units, 50% of deaths are attributed to MOF (76). Ischemia-reperfusion injury in any organ can result in SIRS, ARDS and MOF. Neutrophil migration in IRI is an important part of excessive damage in all organs as highlighted in previous sections, and reverse migration has been related to systemic inflammation after remote IR events. Woodfin and colleagues (77) demonstrated this event in a mouse model that initiates IRI in the cremaster muscle or lower limb. Using three-dimensional and four-dimensional imaging technology, they observed downregulation of JAMC, which usually prevents reverse migration and transendothelial neutrophil migration, which is depicted in Figure 3. Neutrophils that undergo reverse

![Mouse epithelium showing neutrophil infiltration](image_url)

**Fig. 2.** Mouse epithelium showing neutrophil infiltration. Intestinal IRI increases granulocytic neutrophil infiltration in the intestine, accompanied with destruction of villi (loss of epithelial integrity). Representative sections of ileum from (A) sham-operated wild-type mice (WT-SHAM) mice and (B) intestinal IR wild-type mice (WT-IR) showing infiltrating neutrophils (stained red/pink) in the villi of small intestine as indicated by arrows. Granulocytic neutrophils were identified by staining specific leukocyte esterases. The WT-IR mice were subjected to IR surgery in which the superior mesenteric artery was ligated for 30 min and released (reperfused) for 150 min. The WT-SHAM mice underwent the same surgery procedures without the artery being ligated. Tissues were collected, paraformaldehyde fixed, and postprocessed for the esterase stain (unpublished data, 2013).
migration exhibit enhanced ROS generation and more resistance to apoptosis, contributing to systemic inflammation and secondary organ damage (77). Further support for the role of these neutrophils in MOF is a clinical trial analyzing the role of neutrophils in the circulatory and lymphatic system of mesenteric IRI. Disruption of the tight junctions increased vascular permeability. This enabled neutrophils and enteric bacteria to translocate into the circulatory and lymphatic systems. Neutrophils now primed for enhanced ROS production damage remote organs, which is highly attributed to ARDS and MOF (1). These findings further substantiate the need for a therapeutic that can reduce the excessive inflammatory response caused by IRI and show how critical neutrophils are in IRI.

Neutrophil targeting therapeutics to treat IRI

To date, most therapeutics have targeted cytokines, complement, free radicals, platelet-aggregating factor, and adhesion molecules in an attempt to resolve the adverse effects of IRI. So far, such agents have been relatively ineffective clinically (11, 60, 69). Current therapeutic options for IR are merely palliative, offering some relief to the patient’s discomfort, but failing to improve the underlying condition (78).

Several animal studies supplemented with antioxidants demonstrated reduced IRI, and therefore one trialed treatment for IRI has been to increase the levels of NO before surgery as NO regulates ROS (79). During an ischemic state, production of NO is interrupted. Upon reperfusion, the ischemic tissue is overloaded with superoxides that quench any remaining NO and inactivate further production and produce highly toxic peroxynitrite (16). Unfortunately, increasing levels of NO in tissue before ischemia exacerbated IRI (7). Alternate antioxidant treatments such as allopurinol, superoxide dismutase, iron chelators, N-acetyl cysteine, ethanol, captopril, and verapamil have also failed to provide conclusive evidence for clinical end-point success in animal and clinical trials (80, 81). 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 (82) and has had success in a clinical pilot study of acute myocardial infarction (83). Recently, stobadine, a novel synthetic pyridindole antioxidant, which diminishes lipid peroxidation and protein impairment by free radical scavenging and antioxidant activity, has been shown to provide significant protection from IRI in rat kidneys (44). Based on evidence showing hydrogen sulfide (H2S) as a modulator of inflammatory events through interaction with leukocytes (84), Sivarajah and colleagues investigated its role in myocardial IR. They demonstrated that H2S decreases myocardocyte apoptosis and ICAM-1 expression and neutrophil infiltration (13).

Initial success has been established in preclinical models of IRI for a handful of therapeutics that target neutrophils. A monoclonal antibody targeted against the CD11/CD18 integrin showed promising results in animal models (85–87), but clinical trials failed to show a significant reduction in infarct size (88, 89). G protein-coupled receptors have been very successful for a range of disorders and account for almost a third of all prescription drugs in current use (90). Evidence to date indicates they may also be successful targets for IRI. G protein-coupled receptor 43, which is highly expressed on neutrophils (91), is a receptor for short-chain fatty acids. These have shown to reduce the degree of IRI in rat gut using a model of mesenteric IR (92). Therefore, modulation of neutrophils through G protein-coupled receptor 43 could be a possible future avenue to modulate neutrophil recruitment to organs following IRI. Another G protein-coupled receptor, adenosine 2A (A2A) receptor, also has protective effects. It reduced infarct size in a pig model of myocardial IRI (93) and inhibited adhesion molecules on endothelial cells and reduced neutrophil numbers in a mouse model of kidney IRI (94).

Complement inhibition is another attractive target. Gut, liver, kidney, limb, and brain models have revealed the role of...
complement as a key mediator of postischemic damage (95, 96). Further studies supplement these findings, showing that complement inhibitors such as recombinant scfR1 do reduce IRI in various organs (2, 72, 97–100). However, complement inhibitors have the drawback that they have to block tissue injury while preserving its function to prevent infection and eliminate immune complexes; failure to do this leaves the patient severely immunocompromised and susceptible to infection (101). To date, eculizumab is the only clinically available therapeutic that specifically targets the complement system and is approved for use in paroxysmal nocturnal hemoglobinuria and atypical hemolytic-uremic syndrome (102). It specifically targets C5, preventing its cleavage into C5a, a potent chemoattractant, and C5b, which forms membrane attack complex. C5a is an important chemoattractant for neutrophils, and therefore blocking C5 could reduce neutrophil infiltration in IRI. Unfortunately, pexelizumab, a close analog to eculizumab that also inhibits cleavage of C5, failed to reduce infarct size in a human myocardial infarction trial (103). In animal models where IR is induced, complement depletion significantly reduces neutrophil numbers and decreases lung permeability (104). Hence, there is a strong possibility that reduction of IRI when inhibiting complement is actually due to a reduction in neutrophil infiltration, inferring that a therapeutic intervention that targets neutrophils specifically could be the key to preventing IRI. In support of this hypothesis, we recently demonstrated that infusion of C3a agonist peptide to mice reduced neutrophil mobilization after intestinal IRI, which resulted in reduced tissue neutrophil infiltration and ameliorated disease pathology (23).

Future trends

Many failures have been observed in an attempt to prevent and treat IRI. These failings could be due to a number of reasons, from a lack of understanding of the pathophysiology to insufficiency of the disease models. A main hurdle in drug development is the translation of the efficacy in animal models to humans. Clinical trials for therapeutics that target inflammatory responses have been particularly fruitless in the treatment of IRI, with promising in vivo data in animal models failing to relate clinically. The success of therapeutics could be restricted by the availability of models that can truly reflect in vivo biology, which has been highlighted recently in a number of reviews (105–107). Furthermore, current studies generally use or target only one component that impedes activation or migration of neutrophils. Targeting several key factors at the same time could provide better protection from IRI without compromising any area of the immune system and thus resulting in better patient outcomes.

In reality, the insult from IRI is multifactorial, and a therapeutic that targets a single molecular aspect of pathology will most likely continue to be ineffective. As such, therapeutics should aim to target multiple pathways, or indeed whole cells such as the neutrophil, to maximize the impact of reducing the inflammatory response caused by IRI. IRI can occur in just about every part of the body and has a plethora of etiologies that are specific to the initial insult, area, and organ in which it takes place. Regardless, it is apparent that all mechanisms lead to recruitment and activation of neutrophils, which have been shown to correlate with disease severity. Therefore, the ultimate therapeutic or combination of therapeutics would ideally dampen the inflammatory signals that mobilize and recruit neutrophils or regulate neutrophils directly in order to prevent IRI from developing.

CONCLUSIONS

IRI is common during various traumatic and surgical events and responsible for ARDS and MOF, which causes death in more than half of all patients affected. Various strategies have been used to prevent the adverse effects of IRI, but the complex pathophysiology of IRI continues to evade treatment. The inflammatory response is indubitably a key mediator of IRI. In addition, this review has emphasized the importance of neutrophils as a significant contributor to the progression of IRI. Neutrophils contribute to the severity of IRI by exacerbating ischemia through blockage of capillaries (no-reflow phenomenon), escalating the inflammatory response by releasing cytokines, damaging cells unaffected by ischemia through release of ROS, and, potentially most significantly, by disrupting the endothelial and epithelial barriers, which leads to MOF. Therapeutics have targeted several pathways involved in the pathophysiology of IRI but so far have failed to provide an effective therapy to ameliorate outcomes. This review has highlighted the underlying and necessary role of neutrophils in IRI. Further understanding of the mechanisms involved in mobilization, transmigration, and activation of neutrophils in IRI could lead to a potential therapeutic target that can prevent the onset of IRI.

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