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The Cytokine Network in Acute Renal Failure

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Over the past decade, primarily in experimental models, considerable gains have been made in deciphering the critical role of inflammation in the pathogenesis of acute renal failure (ARF). These gains notwithstanding, the therapeutic goal of preventing and successfully reversing ARF in humans remains unfulfilled. Acute renal failure is a clinical syndrome characterized by an acute kidney injury that, over the course of hours to days, results in an abrupt decline in glomerular filtration rate (GFR), and the accumulation of nitrogenous waste. In the United States (US), ARF represents a common and important health problem in hospitalized patients, with a steadily rising incidence,¹ and a high fatality rate.² The lack of improvement in clinical outcomes over the past several decades has been ascribed, in part, to increasing patient age and a high prevalence of comorbid conditions, including pre-existing chronic kidney disease in up to 30% of patients.² This issue of *Nephrology Rounds* summarizes the experimental and clinical data supporting the role of cytokines in ischemic, nephrotoxic, and sepsis-mediated ARF, and critically appraises association studies on cytokine gene polymorphism and ARF. Future directions are considered, including the emerging role of novel biomarkers and imaging techniques for early detection of acute kidney injury, the use of genomic medicine for risk stratification, and the prospect of cytokine-modulating preventive and treatment strategies for ARF.

SIRS and CARS

An acute inflammatory state is characterized by an initial pro-inflammatory response, known as the systemic inflammatory response syndrome (SIRS), which is geared towards recruitment of inflammatory cells to sites of injury. A subsequent anti-inflammatory response, known as the compensatory anti-inflammatory response syndrome (CARS), is aimed at limiting tissue injury and promoting healing. Bacterial sepsis is the most common cause of SIRS in hospitalized patients and, in the US, its incidence is steadily rising.³

The pathogenesis of sepsis begins with the proliferation of bacteria at a nidus of infection that spreads slowly into contiguous tissues. The microorganisms may then invade the bloodstream, leading to bacteremia, or they may proliferate *in situ*, leading to the release of various substances into the bloodstream. These substances include both structural components of the microorganism and extracellular enzymes and exotoxins that, in turn, induce the release of endogenous host mediators of sepsis from plasma precursors or cells. The initial interaction of bacterial products with monocytes results in the release of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6).⁴ These substances interact with the vascular endothelium and stimulate the synthesis of platelet-activating factor, arachidonic acid metabolites, and nitric oxide, resulting in arterial vasodilatation, hypotension, and organ dysfunction. Furthermore, interleukin-8 (IL-8) promotes the recruitment of neutrophils to inflammatory sites, where the release of toxic cellular substances, including reactive oxygen species (ROS) and proteolytic enzymes, significantly contribute to parenchymal injury. Interleukin-6 also induces an acute phase reaction, and both TNF- α and IL-6 stimulate protein catabolism and loss of lean body mass.

The CARS phase is characterized by the production of anti-inflammatory monocyte-derived molecules, including interleukin-10 (IL-10), IL-1 receptor antagonist (IL-1Ra), and soluble TNF receptor (sTNF-R).⁵ Interleukin-10 is the most potent anti-inflammatory cytokine and its release by monocytes is delayed relative to that of pro-inflammatory cytokines, resulting in the suppression of TNF- α , IL-1 β , and IL-6 synthesis.⁵ IL-1Ra is



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mainly secreted by monocytes in response to other cytokines and microbial components, and acts by binding to the IL-1 receptor without transducing an intracellular signal. Endogenous IL-1Ra is important to host defense in inflammatory states;⁶ in fact, a 1,000-fold excess of IL-1Ra is required to block the hemodynamic effects of IL-1 β . Consequently, the balance between pro-inflammatory cytokines such as TNF- α and IL-1 β , and their specific inhibitors, IL-10 and IL-1Ra, respectively, may be critical in determining the extent of the inflammatory response. The balance between the proinflammatory cytokines and their specific inhibitors may also have an important influence on outcomes in patients suffering from an acute inflammatory disorder.

Role of cytokines in ischemic and nephrotoxic ARF

Although systemic or renal hemodynamic insults are important in the pathogenesis of ARF, increasing evidence supports a critical role for inflammatory mechanisms in the pathogenesis of ARF following both ischemic and nephrotoxic injury.⁷ In a mouse model of whole body ischemia, ARF is characterized by inflammation with increased renal myeloperoxidase (MPO) levels, and gene expression of intercellular adhesion molecule-1 (ICAM-1), and IL-6.⁸ This inflammatory response, as well as the development of ARF, is partly reduced in T-cell deficient mice,⁸ arguing for the importance of these cells in the pathogenesis of ARF following ischemia-reperfusion injury. These emerging data indicate the relative importance of T-lymphocytes in the pathophysiology of ischemic ARF.⁹

In a mouse model of cisplatin nephrotoxicity, ARF is characterized by the activation of proinflammatory cytokines such as TNF- α and IL-1 β , and chemokines such as monocyte chemoattractant peptide-1 (MCP-1).¹⁰ The use of pentoxifylline, an inhibitor of TNF- α production, or a TNF- α monoclonal antibody blunts cisplatin-induced increases in TNF- α and IL-1 β expression and reduces TNF- α urinary levels.¹⁰ In addition, TNF- α inhibitors ameliorate cisplatin-induced renal dysfunction and reduce structural damage. Similarly, TNF- α -deficient mice are resistant to cisplatin nephrotoxicity.¹⁰ In another model of cisplatin-induced ARF, TNF-Receptor-2 (TNF-R2)-deficient mice develop milder renal dysfunction and, morphologically, display reduced necrosis, apoptosis, and leukocyte infiltration into the kidney compared with either TNF-R1-deficient or wild-type mice.¹⁰ In contrast, in an experimental model of endotoxin-induced ARF, the kidney injury appears to be mediated by TNF- α acting on the TNF-R1.¹¹ Taken together, these results indicate that TNF- α plays a central role in cisplatin-induced inflammatory responses in the kidney and, in mice, TNF-R2 participates in cisplatin-induced renal injury,¹⁰ whereas TNF-R1 participates in endotoxin-mediated injury.¹¹

The role of anti-inflammatory strategies in limiting tissue injury is emerging. For example, the administration of IL-10 inhibits the expression of TNF- α , ICAM-1, and

inducible nitric oxide synthase in an experimental model of ischemic and nephrotoxic injury and it improves renal histology.¹² Antibody to ICAM-1 protects the kidney against ischemic and nephrotoxic injury.¹³ The administration of IL-10 also inhibits macrophage-mediated injury in experimental glomerulonephritis by inhibiting MCP-1, IL-1 β , and ICAM-1 expression.¹⁴ Finally, IL-10 gene transfer significantly attenuates glomerular lesions and ameliorates kidney function in experimental crescentic glomerulonephritis.¹⁵

Role of cytokines in sepsis-associated ARF

ARF often develops in the setting of sepsis, and microbial and host inflammatory mediators play a critical role in mediating renal injury.¹⁶ The initial “cytokine storm” is initiated by a number of factors, including bacterial products, ischemia-reperfusion, complement activation, and the redundant effects of other cytokines and host inflammatory modulators. This results in leukocyte activation along with the expression of adhesion molecules and the production of various biologically-active substances. This pro-inflammatory cascade contributes to endothelial injury of the renal microvascular bed,⁴ leading to the development of ARF.

In addition, activated neutrophils, trapped in the kidneys through recruitment by IL-8, secrete mediators that further contribute to tubulo-interstitial injury.¹⁷ These findings have important implications because activation of complement and neutrophils by contact between blood and cellulose-based dialysis membranes delays recovery of renal function in an experimental model of ischemic ARF and this is accompanied by more intense neutrophil infiltration of *vasa recta*.¹⁸ Taken together, these findings suggest that, clinically, the extent and speed of recovery from ARF might be improved by the use of more biocompatible dialysis membranes.

Histopathology of leukocytes in ARF

Experimental data suggest that following ischemia-reperfusion injury, infiltration of inflammatory cells into the kidney consists primarily of neutrophils and platelets in the initiation phase, macrophages in the extension phase, and T-lymphocytes in the repair phase.¹⁹ Morphological studies of acute tubular necrosis in humans demonstrate a preponderance of neutrophils in the *vasa recta* and the interstitium in the early stages of ARF.^{19,20} These transient pathological findings are rarely appreciated in the clinical setting, since neutrophils are quickly cleared from sites of injury. Indeed, neutrophils rapidly undergo apoptosis and are engulfed by tissue macrophages, or they egress from sites of injury.²¹ Peri-tubular granulomas have also been observed in later stages of established ARF, lending some credence to the role of T-lymphocytes in such histopathological formations, and possibly in the repair phase of human ARF. Taken together, these data clearly support a role for inflammation in ARF, a condition that has often been thought to be non-inflammatory and continues to be infrequently biopsied.

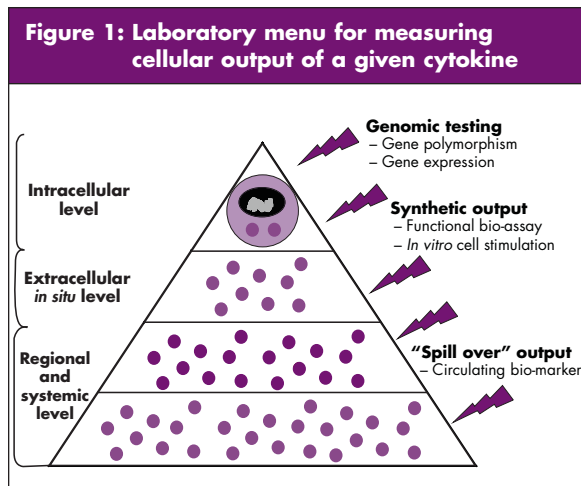
Cytokine measurements in human ARF

In humans, studies linking plasma cytokine levels to the risk of ARF and adverse clinical outcomes have demonstrated conflicting results. In one study, high plasma IL-6 and IL-10 levels predicted hospital mortality among patients with ARF.²² Another study failed to demonstrate a predictive value of plasma IL-6, IL-8, and IL-10.²³ In patients with septic shock, elevated circulating levels of sTNF-R1 and TNF-R2 predicted the development of ARF and hospital mortality.²⁴ In another study of septic patients, an elevated plasma IL-6-to-IL-10 ratio was associated with a higher prevalence of multiple organ failure, supporting the hypothesis that, in sepsis, impaired or delayed IL-10 responses might contribute to organ dysfunction.²⁵ Circulating IL-10 levels are extremely labile in humans and display monophasic responses to TNF- α administration. Paradoxically, elevated levels of circulating IL-10 have also been shown to correlate with adverse outcomes in patients with sepsis.²⁶ However, this is consistent with the anti-inflammatory role of IL-10, which is normally produced in response to the initial pro-inflammatory “cytokine storm,” and acts to diminish transcription and synthesis of TNF- α and other pro-inflammatory cytokines. Therefore, a measurable circulating IL-10 level might simply be a surrogate marker for the extent of SIRS. Consequently, assaying directly for cellular output is likely to be a more reliable measurement of cytokine modulation and such measurements have been reported in patients with ARF. For example, *ex vivo* TNF- α and IL-10 total synthetic output by endotoxin-stimulated monocytes has been shown to be impaired in patients with ARF,²⁷ and intracellular TNF- α , IL-1 β , IL-6, and IL-8 content in endotoxin-stimulated monocytes is markedly reduced in critically ill patients with ARF compared to healthy subjects.²⁸

Cytokine measurement pitfalls

Several pitfalls regarding cytokine measurements are worthy of mention. Extracellular cytokine release is episodic and transient, and *in situ* cytokine levels tend to be higher than systemic levels. In addition, intracellular cytokines can exert juxtacrine effects. Finally, bioassays for circulating cytokines are suboptimal due to the presence of natural inhibitors. Examples include sTNF-R and sIL-1R that bind TNF- α and IL-1 β , respectively; α -2-macroglobulin that binds circulating IL-1 β and IL-6; and erythrocytes that bind circulating IL-8.

Figure 1 displays the available “laboratory menu” for measuring the cellular output of a given cytokine. At the cellular level, genomic testing, including single nucleotide polymorphism and microarray techniques that allow high throughput analysis of cytokine genes, are likely to be the most sensitive and specific. The synthetic output of a given cytokine may be assessed indirectly by using functional bioassays, or directly by measuring the intracellular synthesis or extracellular release of the biomarker under unstimulated conditions, or following *in vitro* cell stimula-



tion. The most distal and likely the least reliable measurements are peripheral cytokine levels, as mentioned in the former section.

Future directions

Novel biological markers for early detection of ARF

Novel biological urinary markers for the early detection of acute kidney injury are slowly emerging.²⁹ Promising examples include the kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), and N-acetyl- β -D-glucosaminidase (NAG).

- While the role of urinary cytokines and other biomarkers of kidney injury remain unknown, a recent study demonstrated the detection of the soluble form of human KIM-1 in the urine of patients with biopsy-proven acute tubular necrosis.³⁰ This transmembrane protein is expressed by the human renal proximal tubule and has been proposed as a useful biomarker for renal proximal tubule injury to facilitate the early diagnosis of ARF.³¹

- NGAL, a protein that is upregulated in tubular epithelial cells undergoing proliferation, has also been proposed as both a urinary and plasma biomarker for ischemic renal injury.^{32,33} Although the role of NGAL in the kidney remains poorly understood, it may play a renoprotective role in ischemic ARF.³⁴

- Another promising molecule is IL-18 which is markedly elevated in the urine of kidney transplant recipients who suffer from delayed renal graft function due to prolonged cold ischemia.³⁵

- Finally, in patients with ARF, urinary NAG has been shown to correlate with urinary cytokine levels,³⁶ disease severity, and adverse outcomes.³⁷

Novel imaging techniques for early detection of ARF and inflammatory infiltrates

There is a need to develop novel imaging techniques for the early diagnosis of ARF, as well as non-invasive tools to help detect inflammatory infiltrates in ARF.³⁸ The use of polyamine dendrimer-based magnetic resonance

imaging (MRI) contrast agents to image early renal tubular damage is one such example that was recently validated in a mouse model of ischemia-reperfusion injury.³⁹ Ultra-small super-paramagnetic iron oxide (USPIO) enhanced MRI is another emerging technology that can detect inflammation in experimental ischemic and nephrotoxic ARF and in acute kidney transplant rejection.^{38,40} In this technique, the USPIO particles are internalized by leukocytes, and once internalized, MRI signal intensity decreases on T₂-weighted images. Taken together, these promising novel tools await investigation in humans.

Genetic risk assessment and stratification tools

While the above data support the role of cytokines as important mediators of parenchymal injury in ARF, the role of genetic factors affecting cytokine production and their implications for ARF have remained largely unexplored. Such novel genetic risk assessment and stratification tools are likely to become the focus of future research efforts and cytokine genotype profiling is a good example.¹⁶

One approach to identifying genes relevant to human disease is based on association studies that identify susceptibility genes for common polygenic diseases. This “candidate gene” approach relies on biological plausibility to identify highly likely candidate genes. In this analytical approach, environmental factors play a critical role in disease expression. An example includes the study of genes encoding for cytokines in ARF. Positive associations between cytokine gene polymorphisms and ARF are slowly emerging in the literature, as summarized in the next section.

The TNF- α gene is located on the short arm of chromosome 6. Polymorphisms within the 5'-flanking region of the TNF- α gene at positions -238 (G to A) and -308 (G to A) have been reported, and the -308 A-allele, also referred to as the TNF- α 2 allele, has been associated with high promoter activity.¹⁶ Moreover, the TNF- α 2 allele has been found to correlate with enhanced spontaneous and stimulated TNF- α production both *in vitro* and *in vivo*.¹⁶ In one study of patients with ARF who require dialysis, carriers of the -308 TNF- α A-allele had higher TNF- α production by endotoxin-stimulated leukocytes, a higher APACHE II score, and a higher risk of death.⁴¹ This allele has also been associated with an increased risk of ARF among pre-term neonates.⁴²

The IL-6 gene is located on the long arm of chromosome 7. A polymorphism has been identified within the 5'-flanking region of the IL-6 gene at position -174 (G to C) and -572 (G to C).¹⁶ The -174 C polymorphic allele is associated with decreased IL-6 transcription and lower circulating IL-6 levels.¹⁶ In contrast, carriers of the wild-type

IL-6 -174 G allele have higher serum IL-6 levels.¹⁶ The low IL-6 producer genetic variant has been associated with an increased risk of ARF in pre-term neonates.⁴² This is not inconceivable since IL-6 has both pro- and anti-inflammatory properties. A recent study demonstrated that the co-existence of the -308 TNF- α A-allele and the -572 IL-6 C-allele in Caucasian patients undergoing cardiac surgery is associated with the development of severe postoperative ARF,⁴³ arguing that this constitutes a high-risk pro-inflammatory polymorphism combination.

The IL-10 gene is located on the long arm of chromosome 1. IL-10 production is genetically determined and controlled at the transcriptional level. The IL-10 5'-flanking region, which controls transcription, is polymorphic with a single-base-pair substitution at position -1082 (G to A).¹⁶ *In vitro* studies have identified 3 phenotypic secretion levels for IL-10 based on allelic substitutions (G to A) at the -1082 position.¹⁶ These findings have been confirmed by transient transfection studies.⁴⁴ Additional polymorphisms at positions -819 (C to T) and -592 (C to A) have been described, but have been variably linked to regulation of gene transcription.¹⁶ Polymorphisms at these 2 sites are in linkage disequilibrium. In one study, carriage of the IL-10 -1082 G-allele among patients with ARF requiring dialysis was associated with higher IL-10 production and a lower risk of death after adjustment for APACHE II score and sepsis.⁴¹ In addition, the co-existence of the -308 TNF- α A-allele and the -1082 IL-10 AA genotype (associated with low IL-10 production levels) was associated with the worse outcome,⁴¹ arguing that this constitutes yet another high-risk cytokine gene polymorphism combination.

Several limitations of polymorphism-association studies are worthy of mention. Traditionally, they consist of case-control studies and are constrained by small sample sizes with chance accounting for the results. Therefore, they must be interpreted with caution, especially when biologic plausibility has not been determined or is unknown. A better understanding of genetically-linked polymorphisms may be critically important since the polymorphism of a particular gene may just be a marker for another, yet to be identified, disease-causing sequence variant. This more comprehensive approach requires the use of linkage analyses and a good understanding of neighboring candidate genes located on the same chromosome. Finally, an important criterion that has been proposed for the study of genetic polymorphism-association studies is the reproduction of results in different populations.¹⁶ The future of genetic studies in ARF will require large, prospective, cohort studies with careful phenotypic characterization and the development of risk stratification tools to aid targeted therapies.

Table 1: Therapeutic modulation strategies for TNF- α and IL-10

Strategy	Mode of action
Down-regulation of TNF-α	
Dexamethasone	Reduces TNF- α transcription & synthesis
Pentoxifylline	Reduces TNF- α synthesis
Interleukin-10	Reduces TNF- α transcription and synthesis
Anti-TNF- α monoclonal antibody	Neutralizes circulating TNF- α
Soluble TNF receptor	Neutralizes circulating TNF- α
Thalidomide	Promotes TNF- α mRNA degradation
Somatostatin	Down-regulates TNF- α receptor
Up-regulation of IL-10	
Dexamethasone	Increases IL-10 transcription and synthesis
Theophylline	Increases IL-10 transcription and synthesis
Cyclosporin A	Increases IL-10 transcription and synthesis
FK-506	Increases IL-10 transcription and synthesis

Targeted cytokine-modulating therapies

In the past decade, human sepsis trials using anti-cytokine strategies have been disappointing, partly due to the enormous complexity of sepsis pathogenesis and the futility of attempts to block a single inflammatory mediator, while ignoring the interplay of different biologically active mediators.⁴ Nevertheless, in the 21st century, there is likely to be renewed interest in targeted therapies for ARF, including the modulation of 2 particular cytokines, TNF- α and IL-10 (Table 1).⁴⁵ This renewed interest emanates from the current availability of several cytokine inhibitors for the treatment of chronic inflammatory disorders. The advent of genomic medicine, if conducted properly and ethically, has the potential to help stratify patients who are most likely to benefit from a cytokine-modulating strategy. This strategy will likely become the focus of pharmacogenomic approaches for the prevention of predictable acute insults to the kidney, such as exposure to radiocontrast agents or cardiopulmonary bypass surgery.

Conclusion

The pathobiology of ARF is the product of many genes acting concomitantly. Gene activation patterns likely determine the extent of tissue injury and repair. Genetic polymorphisms may help stratify high-risk patients, target populations in clinical trials based on genotype profiles, and design “custom drugs.” Novel biomarkers and imaging techniques will likely improve early recognition of acute kidney injury. However, the long-term challenges of this endeavor

include the logistical barriers of drug delivery to kidney parenchyma and the optimal timing of drug administration.

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