Targeting Inflammation in So-Called Acute Kidney Injury

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Summary: The clinical category of acute kidney injury includes a wide range of completely different disorders, many with their own pathomechanisms and treatment targets. In this review we focus on the role of inflammation in the pathogenesis of acute tubular necrosis (ATN). We approach this topic by first discussing the role of the immune system in the different phases of ATN (ie, early and late injury phase, recovery phase, and the long-term outcome phase of an ATN episode). A more detailed discussion focuses on putative therapeutic targets among the following mechanisms and mediators: oxidative stress and reactive oxygen species–related necroinflammation, regulated cell death–related necroinflammation, immunoregulatory lipid mediators, cytokines and cytokine signaling, chemokines and chemokine signaling, neutrophils and neutrophils extracellular traps (NETs) associated neutrophil cell death, called NETosis, extracellular histones, proinflammatory mononuclear phagocytes, humoral mediators such as complement, pentraxins, and natural antibodies. Any prioritization of these targets has to take into account the intrinsic differences between rodent models and human ATN, the current acute kidney injury definitions, and the timing of clinical decision making. Several conceptual problems need to be solved before anti-inflammatory drugs that are efficacious in rodent ATN may become useful therapeutics for human ATN.

Keywords: AKI, injury, regulated necrosis, necroptosis, neutrophil extracellular traps, therapy

In a world of growing complexity, the field of nephrology decided to simplify the range of growing knowledge and evidence into two spheres: acute kidney injury (AKI) and chronic kidney disease (CKD). This oversimplification came with brainwashing that resulted in a series of misconceptions blocking scientific and translational progress. One major misconception is that the current definition of AKI bases injury not on injury markers, but on functional parameters.[1–3] Urinary output and serum creatinine (SCr) provide a signal only after more than 50% of nephrons are dysfunctional. This is in sharp contrast to CKD, in which proteinuria deriving from maybe a few injured glomeruli already can indicate kidney disease. This is not the case in AKI. The current definition of AKI entirely excludes certain acute kidney injuries such as unilateral renal colic and, therefore, compromises a broad appreciation of AKI being a potentially well-treatable disease (Fig. 1). In turn, prerenal failure easily fulfils the criteria of AKI, although no injury is present. As such, the epidemiologist's view on AKI is of little meaning. However, many researchers refer to the epidemiology of AKI to then refer to acute tubular necrosis (ATN), ignoring that given the lack of a kidney injury marker–based definition of AKI the true epidemiology of AKI/ATN is unknown.

Therefore, in this review we avoid the term AKI when discussing the role of the immune system in ATN. ATN is a relevant disease entity because ATN can lead to nephron loss. Because the number of nephrons is the main predictor of renal function, renal reserve, and long-term renal outcomes, preventing nephron loss is the first mission of nephrologists. Here, we discuss how the immune system is involved in ATN-related nephron loss and how to select the best therapeutic immunity-related targets to minimize nephron loss and to improve outcomes of patients with ATN.

CONCEPTUAL PROBLEMS IN FINDING TREATMENTS FOR ATN

ATN Recognition Based on SCr and Urinary Output Implies Late Diagnosis

Acute kidney injury currently is based not on early injury markers, but on late-stage markers of kidney excretory dysfunction[1–3] (Fig. 1). Any therapeutic intervention intended to abrogate the inflammatory phase of ATN will have to be administered during the early injury phase, which usually is missed. It would be necessary to implement routine screening using kidney injury markers[4,5] in high-risk patients to identify AKI within a window of opportunity for anti-inflammatory therapy.

Animal Models Have Limits in Predicting Inflammation-Related Targets

Although toxin-induced ATN such as cisplatin nephropathy is similar in rodents and human beings, most

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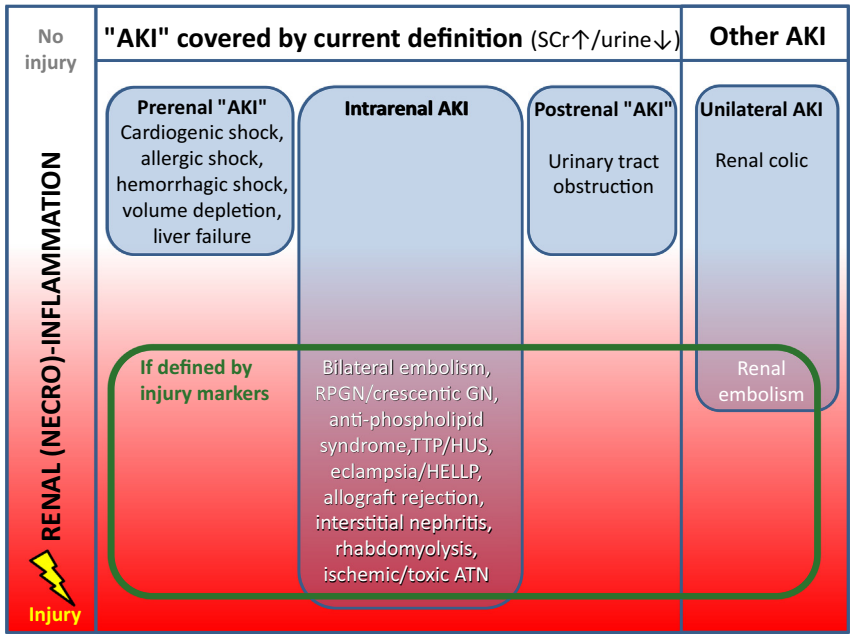

Figure 1. Acute kidney injury and renal inflammation. It is a general misconception that the current classification of so-called AKI is based on injury markers but not on markers of renal function. As a consequence, shock-related renal dysfunction is classified as injury, although the kidney is not affected by any injury but only by hypoperfusion. Consequently, there is little inflammation and necrosis involved in the pathogenesis of so-called prerenal AKI. The current classification of AKI also includes acute postrenal obstruction despite the absence of kidney injury, inflammation, and necrosis. As a second misconception the current classification of so-called AKI does not cover unilateral forms of kidney injury because SCr and urinary output usually remain unaffected in patients with a normal baseline GFR. Nevertheless, some forms of unilateral acute kidney diseases involve true renal cell injury and inflammation necrosis, for example, unilateral renal embolism. Classifying AKI by kidney injury markers would avoid these false concepts. HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic uremic syndrome; RPGN, rapid progressive glomerulonephritis; TTP, thrombotic thrombopenic purpura.

other forms of human ATN have a more complex pathophysiology that is difficult to mimic in rodent models.[6–8] For example, renal pedicle clamping is used frequently in rodents but is a rare cause of ATN in human beings. Nevertheless, data from postischemic ATN often are presented as if representing AKI as a whole. Although simple injury models in young inbred mice are good for studying pathophysiology, they are of little value in mimicking clinical settings.[9] Young inbred rodents of a single sex do not mimic the genetically heterogenous, sex-mixed elderly population affected frequently by ATN. Another experimental drawback is that rodents cannot be dialyzed like human beings to survive severe AKI. As a consequence, sublethal AKI episodes in rodents are too mild to rigorously study the regeneration and long-term outcome phase of clinically relevant severe ATN. Only severe bilateral ATN involves advanced uremia, significant nephron loss, persistent inflammation, and subsequent CKD. Another important reason for the poor predictability of rodent models on drug interventions is the use of different primary end points in rodent and human studies.

AKI Often Represents Underlying CKD

Epidemiologic studies declare AKI to be a disease of the elderly,[10] which is an artifact, related to the SCr criteria of the current AKI definition. Although a 50% loss of nephrons can can not substantially increase SCr in those with a normal baseline glomerular filtration rate (GFR), already minor losses of nephrons will meet the current AKI criteria in those with impaired baseline GFR. Therefore, the clinical diagnosis of AKI is confounded largely by underlying CKD, which presents as a discrepancy between animal experimentation and clinical trials. In addition, the new entity of "CKD upon AKI," which at least finally implements the concept of AKI-related nephron loss,[11] largely depends on baseline GFR (ie, underlying CKD and age).

Lacking a Biomarker of Nephron Number

The clinical approach to AKI is focused on SCr, a composite marker affected by many variables, especially by renal reserve (ie, nephron excess and hypertrophy). Any anti-inflammatory drug intervention is meant to