ACUTE KIDNEY INJURY (AKI) is commonly associated with high mortality and morbidity rates, which strongly depend on the time of the diagnosis to allow therapeutic interventions. Recent studies clearly indicate that routine assessments of kidney function based on serum creatinine and blood urea nitrogen measurements and a fall in urine output are outdated because they fail to identify early stages of renal dysfunction and structural injury (5).

The kidney has a remarkable capacity to withstand insults for an extended period of time. The sensitivities of individual renal cells to injury vary depending on their type, position in the nephron, local vascularization, and the nature of injury. The resulting kidney injury is a product of the interplay between cell dysfunction, cell death, proliferation, inflammation, and recovery. This sequence of events potentially provides time to diagnose and determine the cause of kidney failure in the event that sensitive and specific tests for early kidney injury are available.

In their study, Ramesh and colleagues (8) demonstrated that netrin-1 can be used as an early biomarker of AKI. Netrin-1 is a 50- to 75-kDa laminin-like protein that has been previously recognized as a chemotropic and cell survival factor in nervous system development with possible roles in neovascularization, cell adhesion, and tumorigenesis (3). None of the above indicated that netrin-1 could be used as a biomarker of kidney injury.

According to Ramesh and colleagues (8), netrin-1 is excreted in the urine as early as 1 h after injury and reaches a dramatic 30- to 40-fold increase by 3 h and a peak by 6 h after the insult. Netrin-1 excretion preceded by many hours any increase in blood urea nitrogen and serum creatinine. The presented data demonstrated that netrin-1 satisfies the requirements, which are usually applied to the AKI biomarkers. Such biomarkers are expected to appear very early after the injury and to be sensitive and specific to the kidney. To allow prompt diagnostics, AKI biomarkers optimally should be detected using quick and noninvasive procedures.

The authors tested four types of mouse kidney injury models, including ischemia-reperfusion and three toxic impacts: cisplatin, endotoxin, and folic acid. All of these were shown to induce netrin-1 excretion. This observation clearly makes netrin-1 a biomarker, which is universal for hypoxic and toxic renal injury. The universality of netrin-1 excretion suggests it may be potentially applicable to various types of AKI, including cases with unknown causes of AKI.

The magnitude and the significance of rapid netrin-1 excretion induced by kidney insults make it outstanding among all known renal injury markers, including previously described neutrophil gelatinase-associated lipocalin (4), IL-18 (7), kidney injury molecule-1 (1), N-acetyl-glucosaminidase (9), cysteine-rich protein 61 (6), hepatocyte growth factor (10), meprin Aβ (2), and exosomal fetuin-A (11). Importantly, the mode by which netrin-1 reacts to AKI differs from all of the previously known markers. Urinary levels of netrin-1 return back to normal level during reperfusion, suggesting that it also can be used as a prognostic marker for renal recovery, which would significantly increase its clinical value.

Ramesh and coauthors (8) also examined the importance of netrin-1 as a marker for acute renal failure of various etiologies in humans. While it was undetectable in urine of healthy volunteers, the overwhelming majority of patients had dramatically increased urinary netrin-1.

Since netrin-1 already looks like an unusual marker, this finding not only adds to the list of potential markers but strengthens the concept that a panel of markers may be the best solution to predict, diagnose, and monitor the loss of kidney function. It would be interesting to test whether netrin-1 is a predictive biomarker for delayed graft function following kidney transplantation, hypotension due to hemodialysis or cardiovascular surgery, and various nephrotoxicant- or sepsis-induced renal injuries. In addition, urinary netrin-1 may be potentially useful for identifying the type of injured cells and determining the nephron segment affected by the injury.

It is very likely that netrin-1 is mechanistically linked to renal injury since its release is so rapid. However, the exact mechanisms will need to be a subject for further studies. Ramesh et al. (8) showed that renal injury caused an elevation of netrin-1 in tubular epithelial cells; however, netrin-1 mRNA was not induced. Thus the increased urinary excretion of netrin-1 seems to be caused by an induction of protein synthesis and the release of presynthesized protein. The authors suggested that netrin-1 facilitates cell proliferation and regeneration in response to injury and thus may be a marker of renal recovery. Therefore, it is also very likely that netrin-1 has the potential of being used as a therapeutic target to facilitate kidney recovery after injury.

REFERENCES
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