Novel Approaches in the Investigation of Acute Kidney Injury

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Acute kidney injury (AKI) remains a significant health care concern. Many reports describe high mortality rates that largely have remained unchanged for several decades (1,2). With such a poor prognostic outlook, scientists have sought to develop novel therapies that are based on information gleaned from clinical studies as well as *in vitro* and *in vivo* models of renal injury. These approaches have been geared toward understanding molecular, cellular, and physiologic responses of renal injury and have led to a focus on pathways that are related to metabolism, oxidant stress, hemodynamics, inflammation, and growth factors, to name a few, as potential targets of therapy (3).

Will such scientific approaches lead to therapies that bear promise and ultimately affect outcome? Thus far, they have not. It has become clear that a reevaluation of approaches in the study of AKI is at hand, including the incorporation of novel therapeutic approaches, better and more clinically relevant model systems, and the application of better prognostic indicators as a means to establish treatment.

In this issue of *JASN*, two articles represent novel scientific advancement on subjects that have heretofore received little attention in the setting of AKI. In one article, by Broekema *et al.* (4), the fate of bone marrow–derived (BMD) cells was evaluated in a model of ischemia/reperfusion (I/R) injury. These studies were stimulated by interest in the potential to use a cell-based therapy to enhance renal regeneration. Several studies, including a report by these authors (5), have shown that BMD cells have the potential to engraft in regenerating tubules. Nevertheless, the emerging view is that such cells contribute only a small percentage to regenerated tubules (6,7). In contrast, BMD cells may take on other phenotypes in the setting of AKI. Broekema *et al.* describe the expansion of a myofibroblast population after I/R identified by α-smooth muscle actin–positive staining. Using a transgenic rat that expressed human placental alkaline phosphatase as a donor to trace the fate of BMD cells, they demonstrated a significant number myofibroblasts present in the postischemic kidney, approximately 32% of which derived from the bone marrow. These results are consistent with the results of Lin *et al.* (6), who demonstrated that the majority of BMD cells homed to the renal interstitium and expressed interstitial collagens.

The major finding of this study relates to how renal I/R injury alters the kidney with potential long-term consequences. It is worth noting that although the historical viewpoint is that recovery of renal function typically is expected in patients who survive acute renal failure with few secondary problems (8), this perspective increasingly is being challenged. For example, recent data suggest that up to 13% of patients after AKI progress to ESRD within 3 yr; if a pre-existing renal disease is present, then progression to ESRD rises to 28% within the same time period (P. Eggers, National Institute of Diabetes and Digestive and Kidney Disease, personal communication, 2006). Moreover, pediatric patients after AKI have a high predisposition to progressive renal failure. In a recent study, Askenazi *et al.* (9) reported that >50% of pediatric patients showed indications of progressive renal disease and hypertension within 3 to 5 yr of the initial episode. Finally, renal injury in the setting of transplantation (*i.e.*, delayed graft function) represents an independent risk factor for graft survival and the development of posttransplantation hypertension (10–12). These observations suggest that acute injuries to the kidney predispose to chronic complications.

The underlying causes for potential progressive renal dysfunction after recovery from AKI remain unclear. We and others have used rodent models of I/R to investigate the long-term alterations in renal function and have demonstrated the development of secondary renal disease that is characterized by interstitial fibrosis. Among hypotheses that have been proposed, all share the common viewpoint that failure to resolve renal structure or function adequately during the repair process predisposes to secondary chronic renal failure. For example, investigators have proposed that impaired nephron regeneration, combined with compensatory mechanisms, or inflammatory mechanisms may underlie these chronic sequelae (13–15). Work from our laboratory has focused on alterations in vascular structure and have emphasized the possibility that exacerbated local hypoxia may set in motion events that are associated with progressive renal scarring (16). In addition to these possibilities, the early deposition of fibroblasts is of keen interest. Broekema *et al.* clearly demonstrate that a major proportion of these cells derive from the circulation but leave open the possibility that significant numbers of fibroblasts derive from

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tubular or vascular transformation—issues that have yet to be explored directly. From a practical standpoint, this study illuminates that caution is in order for cell-based therapies. When left in a pluripotent state, BMD cells may home to the kidney and take on a more sinister role than desired. On the basis of studies by Togel *et al.* (17) and Arriero *et al.* (18), demonstrating beneficial effects of various mesenchymal stem cells, it seems reasonable to suggest that any future therapy should use cells with a more restricted fate.

A second article published in this issue, by Perianayagam *et al.* (19), has sought to advance the concept that genomics can be used for the diagnosis of AKI. They prospectively evaluated the relationship of single-nucleotide polymorphisms (SNP) in the pro-oxidant p22phox subunit of NADPH oxidase and in the promoter region of antioxidant gene catalase. Whereas polymorphisms in the catalase gene had no effect on AKI, a C to T substitution at position +242 in the coding region of p22phox was associated with greater than two-fold higher odds for dialysis and hospital death. Although hampered by a small sample population, the study is important because it includes AKI of mixed causes and includes the presence of chronic kidney disease. The distribution of genotypes was not different from the general population but affected outcome.

There are at least two important advances with regard to the study by Perianayagam *et al.* First, these data suggest that factors that influence the balance of reactive oxygen species can have an impact on the course of AKI. Such has been suspected for a considerable period of time on the basis of numerous studies using *in vitro* and *in vivo* models (20). On the basis of these data, tailored antioxidant therapy may prove more beneficial in patients with specific alleles of susceptibility. Moreover, clinical trials that are geared toward developing antioxidant therapy should consider mixed genetic background as a variable in efficacy.

The second important advancement is the realization that genomic factors can generate prognostic significance on the course of AKI. This realization can be attributed to the substantial advance in genomic techniques during the past 10 yr, particularly an explosion in the identification of SNP. The potential association of SNP already has received considerable attention in cardiovascular research that is geared toward understanding diseases such as ischemic heart disease and hypertension (21). For example, Casas *et al.* (22) recently published a meta-analysis of 26 studies that investigated SNP alleles in the endothelial nitric oxide synthase gene that is associated with ischemic heart disease and demonstrated a significant risk in at least one allele, the −786/Asp298 allele. However, the study by Perianayagam *et al.* is the first study in which such linkage has been sought in relation to the course of AKI. Given that responses to ischemia in different organs share common molecular pathways that may affect positively or negatively the course of injury, it is not surprising that similar approaches could be extrapolated to AKI in a prognostic manner. Such an approach comes at a welcome time when the search for such indicators increasing is rapidly. It seems reasonable that additional studies that examine other SNP alleles are likely to follow.

The articles contained in this issue illustrate that basic and clinical scientists should continue to generate new approaches to study AKI. It is hoped that by continuing to develop novel approaches, we someday may make inroads to beneficial therapies with an overall effect on outcome.

Disclosures

None.

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See the related articles, "Bone Marrow–Derived Myofibroblasts Contribute to the Renal Interstitial Myofibroblast Population and Produce Procollagen I after Ischemia/Reperfusion in Rats," on pages 165–175, and "NADPH Oxidase p22phox and Catalase Gene Variants Are Associated with Biomarkers of Oxidative Stress and Adverse Outcomes in Acute Renal Failure," on pages 255–263.