Acutely (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, Askennazi 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...
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.

References

15. Chandraker A, Takada M, Nadeau KC, Peach R, Tilney


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.