efficiency is not limited, the destructive inflammatory process (interstitial infiltration of macrophages and expression of proinflammatory mediators) is amplified.

This study strongly supports the hypothesis that PPARα modulates fatty acid metabolism, oxidative stress, apoptosis, and inflammation in the proximal tubule. Thus, PPARα might be considered a novel therapeutic target for fatty acid toxicity associated with proteinuria, as in acute tubular injury after ischemia/reperfusion or cisplatin. Nevertheless, two issues need to be resolved before considering a translational approach. First, species differences have been found in the expression of PPARα and PPAR co-factors; human cells express only 1 to 10% of the amount of PPARα found in rodent cells. In addition, even if mRNA encoding PPARα predominates in human proximal tubular cells, PPARα agonists elicit only a modest activation of peroxisome proliferator response element in these cells, as compared with PPARγ agonists. Thus, the physiologic importance of PPARα expression in human proximal tubules needs further demonstration. Second, in the experiments reported here, Kamijo et al. analyzed the importance of endogenous PPARα rather than the role of synthetic PPARα ligands. Only in preliminary experiments did they observe absent protective effects of clofibrate in wild-type mice that were administered an injection of fatty acid–binding albumin. It is possible that clofibrate treatment was inefficient or even deleterious because the bioavailability of endogenous PPARα ligands is sufficient to activate endogenous PPARα to the maximum. Future work is required to answer this question as well.

DISCLOSURES
None.

REFERENCES


See related article, “PPARα Protects Proximal Tubular Epithelial Cells from Acute Fatty Acid Toxicity,” on pages 3089–3100.

Stem Cells and the Kidney: Where Do We Go from Here?

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The kidney has a remarkable capacity to regenerate and restore its structure and function after acute injury. However, kidney regeneration is frequently delayed or inadequate, resulting in significant morbidity and mortality. Incomplete recovery of

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the injured kidney may lead to progressive loss of renal function over time. Despite advances in our understanding of the cellular and molecular events underlying acute kidney injury (AKI) and regeneration, therapeutic advances have been limited.

Both kidney and circulating stem cells participate in kidney regeneration. However, the role of extrarenal stem cells is at best minimal. The major source of regenerating cells after AKI has traditionally been viewed as less injured, surviving cells that undergo de-differentiation, proliferation, and re-differentiation. Both transgenic and conventional techniques validate the role of surviving cells in kidney regeneration. Discovery of stem cells in adult organs, including kidney, that participate in tissue regeneration has opened new avenues of investigation in regenerative medicine.

The understanding of kidney stem cells is still in its infancy despite rapid advances made in recent years. The kidney is one of the few organs that undergo mesenchymal-epithelial transition during development. Moreover, structures present in the adult kidney arise from reciprocal interactions between two discrete embryonic appendages, namely ureteric bud and metanephric mesenchyme. The adult kidney contains more than 24 mature cell types arranged in distinct vascular, interstitial, glomerular, and tubular compartments. This unique organogenesis and structural complexity of the adult kidney presents many challenges to the identification and characterization of kidney stem cells. The field has been further hampered by the lack of definitive kidney stem cell markers. Without unique markers, adult kidney stem cells are identified on the basis of the broad principles of stem cell biology such as prolonged cell-cycling time (label-retaining cells), ability to extrude Hoechst dye (side population cells), by restrictive cell culture conditions, or by using markers expressed by other stem cells or developing kidney. Existing evidence strongly supports the presence of stem cells in the adult kidney, although this has not been definitively proved and remains a matter of debate. The understanding of overlap between various stem cell populations identified by these distinct strategies is unclear. Given the structural complexity of the adult kidney, the presence of more than one type of stem cell is very likely.

Lazzeri et al. in this issue of JASN identified putative stem cells expressing both CD24 and CD133 in human embryonic kidney that demonstrate stem cell characteristics, such as self-renewal; multilineage differentiation; expression of stem cell transcription factors such as Oct-4, Nanog, and Bmi-1; and the ability to heal the injured kidney. This report is an extension of previous work by these investigators identifying similar cells in adult human kidney localized to the parietal epithelium of the glomerulus. This new study draws on lessons from developmental biology to define markers and to follow distribution of the marked cells during nephrogenesis. They demonstrate progressive restriction of the CD24- and CD133-expressing cells to the urinary pole of Bowman’s capsule with the advancement of nephrogenesis, suggesting this location as a kidney stem cell niche. Other investigators, including ourselves, have demonstrated the existence of stem cells at other locations, including the papilla, proximal tubule, and interstitium.

The investigators have cloned and characterized the cells expressing CD24 and CD133, demonstrating the ability of these cells to undergo multiple population doublings without evidence of senescence or malignant transformation. These cells have the capacity to undergo multilineage differentiation in vitro including the formation of cells expressing markers of different nephron segments. It is interesting that the cells express stem cell markers both in vitro and in vivo. The expression of Oct-4 is particularly intriguing. Oct-4 is a transcription factor expressed in embryonic stem cells, as well as in primordial germ cells in adult gonads. Oct-4 plays a critical role in maintaining pluripotency of embryonic stem cells and the viability of primordial germ cells. More recently, Oct-4—expressing cells have been demonstrated in adult organs, including the kidney, and provide a potential in vivo marker of adult stem cells. It is interesting that induced expression of Oct-4 either alone or in combination with other stem cell transcription factors is sufficient to expand the differentiation potential of somatic cells.

An important finding of this study is the ability of injected CD24- and CD133-expressing cells to reconstitute the injured kidney and improve both structure and function. Cellular therapy in AKI has attracted much recent attention. The use of embryonic stem cells for organ regeneration is limited by formation of teratoma in the host. Lack of teratoma formation by stem cells isolated from the developing kidney is proof of principle that more differentiated stem cells may be safer for therapeutic use. Moreover, committed progenitors that are present in the developing kidney and have predifferentiated toward a kidney phenotype might be better suited for kidney regeneration. The presence of cells expressing both CD24 and CD133 in the metanephric mesenchyme and ureteric bud and their differentiation into cells of either lineage support the concept of a common progenitor cell capable of regenerating the entire nephron. In addition, stem cells identified by Lazzeri et al. can differentiate into vascular and stromal cells. This supports the finding by Oliver et al. of existence in the developing kidney of stem cells that are capable of differentiating into all renal cell types.

Stem cells can repair injured kidney by replacing dead cells, by cell fusion, or by augmenting regeneration of surviving cells by paracrine effects. The contribution of these different mechanisms to kidney regeneration is not clear in this study. The use of human embryonic kidney is surrounded by ethical concerns, making the study by Lazzeri et al. unlikely to be of direct clinical relevance in the near future. However, such studies provide new insights into the mechanisms of kidney regeneration and the role of kidney stem cells in the repair process. In addition to exogenous administration of stem cells, examination of in vitro nephrogenesis from stem cells is likely to provide insight into the mechanism of renal regeneration. Improved understanding of these processes could lead to strategies to protect and kindle endogenous stem cell activity, thereby obviating the need for exogenous administration of stem cells in treating kidney disease.
To move the field of kidney stem cell biology forward, definitive evidence for the presence of adult kidney stem cells is needed. Defining stem cell markers such as Oct-4, Nanog, or dual expression of CD24 and CD133 is important. However, in vivo cell lineage tracking experiments are needed to demonstrate that cells expressing these or other markers can differentiate into different cell types of the normal or injured kidney. Such studies will remove doubts about the existence of adult kidney stem cells and will allow investigators to determine the cellular sources for repair of injured nephrons and the molecular mechanisms controlling this repair. The ultimate goal is to develop therapeutic strategies to enhance the renal regenerative response and lead to improved outcomes in patients with AKI and chronic kidney injury.

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DISCLOSURES

None.

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Towards the Incidence of Acute Phosphate Nephropathy

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In 2003, Desmeules et al. reported a 71-yr-old female who developed acute renal failure after the use of an oral sodium phosphate (OSP) solution as bowel purgative before colonoscopy. Renal biopsy revealed tubular injury and abundant tubular calcium phosphate deposits, suggesting a pathophysiological link between phosphate ingestion and the pattern of renal injury. The authors proposed the term acute phosphate nephropathy (APhN). We subsequently reported 21 cases of APhN,2 and additional case reports have followed.3–6 APhN most commonly occurs in older white females, particularly those with history of hypertension and receiving therapy with renin-angiotensin inhibitors. It is estimated that approximately 14 million screening colonoscopies are performed each year in the United States,7 yet the incidence of APhN remains unknown.

Two large, observational, retrospective studies8,9 in this issue of JASN aim to define that incidence and identify risk factors. The article by Brunelli et al.8 is a retrospective, case-control study of patients undergoing outpatient colonoscopy at three University of Pennsylvania Health System affiliates. It compares patients who subsequently developed acute kidney injury (AKI) to those who maintained normal renal function. AKI was defined by either a 25% or a 0.5-mg/dl increase in serum creatinine over the 6 mo after colonoscopy. Using these criteria, 141 of 2237 patients (6.3%) had AKI. Complete data were available for 116 of the subjects, who were then compared with 349 controls. Risk factors for the development of AKI included female gender, heart failure, and diuretic use. An association between OSP and AKI could only be demonstrated in

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