predominate. Conversely, recent data, including those of Nishio et al.,\textsuperscript{14} suggest that loss of OCD alone is not sufficient to produce a cystic phenotype and that CE along with OCD is required for proper tubule elongation. As such, it will be important to examine the role of CE in various cystic models, such as Fat4.

Many key questions remain unanswered. Given that loss of PKD genes results in PCP-like defects, what is the molecular nature of the genetic interactions between PKD and PCP genes? Do PCP genes control PKD gene activity or vice versa? How are spindle orientation and cell intercalation controlled by PCP and PKD? A deeper understanding of the pathogenic mechanisms that underlie cyst formation in Phkd1, Pkd1, and Pkd2 mutants will hopefully allow targeted therapies to alleviate the morbidity and mortality associated with these devastating diseases.

DISCLOSURES
None.

REFERENCES

Telomere Shortening and Regenerative Capacity after Acute Kidney Injury

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With advances in modern medicine leading to improved health, the percentage of the population who are elderly is increasing. Associated with increasing age is a decline in renal function and loss of renal mass.\textsuperscript{1} These alterations in renal function predict increasing risk for mortality.\textsuperscript{2} The aging kidney also associates with multiple disease states, such as cardiovascular disease,\textsuperscript{3} cancer,\textsuperscript{4} and cognitive dysfunction,\textsuperscript{5} which increase susceptibility to ischemic acute kidney injury (AKI), from which the elderly are less likely to recover.\textsuperscript{6}

Telomere attrition is implicated in many diseases associated with aging, including cardiovascular disease; however, an association between telomere shortening and decreased renal repair and regeneration after injury is largely un-
known. The role of telomeres, repetitive DNA elements located at the end of chromosomes, is to prevent unwanted chromosome shortening and recombination. The length of telomeres is regulated by telomerase, which adds tandem TTAGGG repeats to the end of chromosomes to minimize chromosome shortening. Unfortunately, the majority of human cell types have limited telomerase activity, and, as we age, our telomeres shorten progressively with every cell division, eventually becoming critically short and resulting in senescence and apoptosis. This has serious implications for organ repair, regeneration, and recovery from injury.

In this issue of *JASN*, Westhoff et al. examine the effect of short telomeres on murine renal ischemia-reperfusion injury (IRI) and recovery. One of the problems with using rodent models is that they have longer telomeres than humans. To reduce the length of murine telomeres to mimic that of an aging human, the authors serially intercrossed null mice for the RNA component (Terc) of telomerase. Terc serves as a template for the generation of telomere repeats and is indispensable for the activity of telomerase. Fourth-generation telomerase-deficient mice (G4 Terc−/−) have short telomeres, defects in proliferative organs, and decreased survival. Previous research also indicated these animals have diminished liver regeneration after injury.

IRI was induced in 3- to 4-month-old aged-matched male Terc+/+, G1 Terc−/−, and G4 Terc−/− mice using standard protocols. Telomere quantitative fluorescence in situ hybridization analysis was used to show that G4 Terc−/− mouse kidneys have significantly shorter telomeres compared with Terc+/+ mice. Thirty days after AKI, telomere shortening occurs in Terc+/+ mice and to a greater extent in G4 Terc−/− mice. It should be noted that Terc+/+ and G1 Terc−/− mice do not exhibit decreased renal function on day 7 or 30 after IRI, whereas G4 Terc−/− mice exhibit marked reductions in renal function and regeneration at these time points. These interesting data confirm observations in other injury models and demonstrate that a single renal insult advances the telomere shortening process and repeated injuries may accelerate it.

Three and 30 days after IRI, the amount of apoptosis is also increased in G4 Terc−/− mouse kidneys. The increase in apoptosis is not surprising in light of decreased telomere length. Other laboratories also observe an increased basal rate of apoptosis in aging rodent kidneys, possibly as a result of telomere shortening. Although the G4 Terc−/− mice exhibit an increase in terminal deoxynucleotidyl transferase–DUTP nick-end labeling–positive cells after IRI, the increase reaches only 3% of the observed cells. The authors suggest these low levels of apoptosis were not responsible for the impaired regenerative capacity of the kidneys in mice with short telomeres.

The argument for an important role of senescence in the lack of renal regenerative capacities of the G4 Terc−/− mice after IRI is supported by blunted rates of cellular proliferation. The observed decrease in proliferation is likely due to increased expression of the cell-cycle inhibitors p21 and p16INK4a. Interestingly, p21 levels remain elevated in G4 Terc−/− mice while decreasing in Terc+/+ and G1 Terc−/− mice over time. In contrast, p16INK4a levels on day 30 are elevated in all mice subjected to IRI, with G1 Terc−/− and G4 Terc−/− mice exhibiting greater and equal increases, respectively. Thus, it is likely that mice with short telomeres exhibit impaired regenerative capacity, in part through continued up-regulation of p21. The exact role of p16INK4a in this model is unclear, because both G1 Terc−/− and G4 Terc−/− mice exhibit similar increases on day 30 and only G4 Terc−/− mice exhibit decreased renal function and impaired regenerative capacity.

At day 7 after IRI and beyond, acute histologic damage decreases but tubular deterioration increases and is similar in all groups. By day 30, renal interstitial fibrosis is present in Terc+/+ and G1 Terc−/− mice and is markedly enhanced in G4 Terc−/− mice. Consistent with this observation, numbers of CD3 T lymphocytes do not increase to the same extent in G4 Terc−/− kidneys compared with those from Terc+/+ mice on day 30. It is generally accepted that high levels of fibrosis follow persistent inflammation and that proper interactions between immune cells and fibroblasts are necessary to promote normal tissue repair and prevent excess collagen deposition. Although not addressed by the authors, the diminished T cell response in G4 Terc−/− mice may be connected to chronic renal injury and impaired recovery.

In previous work, Melk et al. hypothesized that increased susceptibility of aging kidneys to acute injury and lack of sufficient repair is due to increased cellular senescence. The use of the Terc−/− mouse allows for a mechanistic examination of the specific role of telomeres in senescence, AKI, chronic kidney disease, and renal repair and regeneration apart from other age-related complications; however, one of the limitations of this study is that all of the animals were young (3 to 4 months of age), and studies using older animals are warranted. Although shortened telomeres may contribute to increased renal injury and decreased renal recovery after an insult, many other factors associated with aging are likely involved, including increased susceptibility to xenobiotics, preexisting cellular and mitochondrial dysfunction, and other disorders including cardiovascular disease and diabetes.

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**DISCLOSURES**

None.
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Uromodulin and Translational Medicine: Will the SNPs Bring Zip to Clinical Practice?

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Tamm-Horsfall protein (THP) was originally described in 1895 as “urinary mucoprotein” and biochemically characterized approximately 50 years ago. Kidney epithelial cells of all placental mammals synthesize THP, and it is the most abundant protein in normal urine.1–2 Pirica, a novel THP-like gene that is induced in response to predation, was recently identified in tadpoles, suggesting that THP family proteins are also present in invertebrate species.3 Uromodulin was originally reported as a unique immunosuppressive glycoprotein from the urine of pregnant women,4 and its amino acid composition is identical to THP.5 Standard nomenclature for THP is now uromodulin.

Uromodulin provides a protein infrastructure for urinary casts used to diagnose various kidney diseases in the clinic. Experimentalists have used both in vitro and in vivo models to define the biology of uromodulin in the urinary tract, and protein chemists have extensively characterized its biochemical properties and domains.6–10 Despite these efforts, the function of uromodulin remains an enigma. Published data suggest uromodulin is glycosyl phosphatidyl inositol-anchored along the apical domain of some kidney epithelia and secreted into urine and blood. It inhibits both bacterial colonization of the urinary track and stone formation, binds and activates leukocytes, and generates the water impermeability of the thick ascending limb of Henle by assembly into filaments through its zona pelucida domain. Tissue distribution of pirica, the amphibian uromodulin-like protein, also supports the hypothesis that uromodulin regulates the water permeability of tissue.3

Mutations in UMOD, the gene that encodes uromodulin, cause rare, autosomal dominant, primary tubulointerstitial