

multiprotein cilia-destined cargo within the cell. Then through association of an adaptor molecule containing a cilia-targeting motif, perhaps such as cystin, multiple proteins deliver to the cilium. Further complexity in this model arises from the fact that not all proteins constitutively localize to cilia but require an external stimulus that promotes cilia entry. A good example of this is Hedgehog signaling. It was recently shown upon binding of Hedgehog to its receptor Patched, the protein Smoothened is targeted to the cilium¹⁴; therefore, multiple targeting motifs and adaptors likely regulate ciliary entry of proteins either in a constitutive manner or in response to a specific cue. Understanding these targeting signals will be key as we continue to unravel the mysteries of the cilia.

DISCLOSURES

This work was supported in part by National Institutes of Health (NIH DK069605) and Polycystic Kidney Disease Foundation (162G08a) grants.

REFERENCES

1. Badano JL, Mitsuma N, Beales PL, Katsanis N: The ciliopathies: An emerging class of human genetic disorders. *Annu Rev Genomics Hum Genet* 7: 125–148, 2006
2. Scholey JM: Intraflagellar transport. *Annu Rev Cell Dev Biol* 19: 423–443, 2003
3. Yoder BK, Hou X, Guay-Woodford LM: The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris, and cystin, are co-localized in renal cilia. *J Am Soc Nephrol* 13: 2508–2516, 2002
4. Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J: Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 33: 129–137, 2003
5. Geng L, Okuhara D, Yu Z, Tian X, Cai Y, Shibazaki S, Somlo S: Polycystin-2 traffics to cilia independently of polycystin-1 by using an N-terminal RVxP motif. *J Cell Sci* 119: 1383–1395, 2006
6. Jenkins PM, Hurd TW, Zhang L, McEwen DP, Brown RL, Margolis B, Verhey KJ, Martens JR: Ciliary targeting of olfactory CNG channels requires the CNGB1b subunit and the kinesin-2 motor protein, KIF17. *Curr Biol* 16: 1211–1216, 2006
7. Mazelova J, Astuto-Gribble L, Inoue H, Tam BM, Schonteich E, Prekeris R, Moritz OL, Randazzo PA, Deretic D: Ciliary targeting motif VxPx directs assembly of a trafficking module through Arf4. *EMBO J* 28: 183–192, 2009
8. Tao B, Bu S, Yang Z, Siroky B, Kappes JC, Kispert A, Guay-Woodford LM: Cystin localizes to primary cilia via membrane microdomains and a targeting motif. *J Am Soc Nephrol* 20: 2570–2580, 2009
9. Hou X, Mrug M, Yoder BK, Lefkowitz EJ, Kremmidiotis G, D'Eustachio P, Beier DR, Guay-Woodford LM: Cystin, a novel cilia-associated protein, is disrupted in the cpk mouse model of polycystic kidney disease. *J Clin Invest* 109: 533–540, 2002
10. Janich P, Corbeil D: GM1 and GM3 gangliosides highlight distinct lipid microdomains within the apical domain of epithelial cells. *FEBS Lett* 581: 1783–1787, 2007
11. Roitbak T, Surviladze Z, Tikkanen R, Wandinger-Ness A: A polycystin multiprotein complex constitutes a cholesterol-containing signalling microdomain in human kidney epithelia. *Biochem J* 392: 29–38, 2005
12. Pazour GJ, Agrin N, Leszyk J, Witman GB: Proteomic analysis of a eukaryotic cilium. *J Cell Biol* 170: 103–113, 2005
13. Tyler KM, Fridberg A, Toriello KM, Olson CL, Cieslak JA, Hazlett TL, Engman DM: Flagellar membrane localization via association with lipid rafts. *J Cell Sci* 122: 859–866, 2009
14. Rohatgi R, Milenkovic L, Scott MP: Patched1 regulates hedgehog signaling at the primary cilium. *Science* 317: 372–376, 2007

See related article, "Cystin Localizes to Primary Cilia via Membrane Microdomains and a Targeting Motif," on pages 2570–2580.

It's about Time: Extending our Understanding of Cardiovascular Risk from Chronic Kidney Disease

Ann Young and Amit X. Garg

Division of Nephrology and Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada

J Am Soc Nephrol 20: 2486–2487, 2009.
doi: 10.1681/ASN.2009101045

It is widely accepted that chronic kidney disease (CKD) associates with accelerated cardiovascular disease and a higher rate of death than would occur otherwise.¹ These associations are based on studies of patients who had low renal function identified at a single point in time or, at most, two measurements separated by 3 mo to confirm chronicity. When caring for patients with CKD, we, too, generally estimate risk on the basis of single time point measurements of renal function. For example, a 65-yr-old man with a GFR of 80 ml/min per 1.73 m² has an estimated risk for death of 12% during the subsequent 5 yr; however, if his GFR is 40 ml/min per 1.73 m², then this risk is at least doubled.¹

In this issue of *JASN*, Shlipak *et al.*² determined whether changes in kidney function during the first 7 yr of the Cardiovascular Health Study associated with increased cardiovascular risk during the subsequent 8 yr. The authors compared 1083 community-dwelling, ambulatory older adults with rapid declines in kidney function to 3295 adults without rapid decline. At baseline, participants were an average age of 72 yr, and 14% had diabetes. The incidence of cardiovascular disease was significantly higher in individuals with rapid declines in kidney function (defined as an annual decline in cystatin C–based eGFR >3 ml/min per 1.73 m²), even after multivariable adjustment for demographics, aver-

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Amit Garg, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada. Phone: 519-685-8502; Fax: 519-685-8072; E-mail: amit.garg@lhsc.on.ca

Copyright © 2009 by the American Society of Nephrology

age kidney function, and established cardiovascular disease risk factors. Specifically, the hazard for heart failure increased by 24% for rapid decliners, whereas for myocardial infarction and peripheral arterial disease, the hazard was 42 and 67% higher, respectively.

Nephrologists naturally appreciate that a more rapid loss of kidney function over time associates with a greater risk for kidney failure. With these results, Shlipak *et al.*² advance the concept that patterns of kidney function over time can also be used to appreciate cardiovascular risk better: A more rapid loss of kidney function associates with greater risk for cardiovascular disease. Whether this is a causal relationship is still a matter of ongoing debate. Of note, patients enrolled in the Cardiovascular Health Study are those typically followed by primary care physicians and not nephrologists, because the average eGFR at the start of follow-up was 79 ml/min per 1.73 m².

Evaluating changes in an exposure, such as kidney function over time, also represents a change in modern epidemiology. Traditionally, exposures have been modeled as static conditions, assessed at a single point in time. In the case of CKD, people with declining kidney function are classified in the same risk group as those with diminished but stable renal function. However, exposures of interest to epidemiologists are, in truth, seldom constant.³ Some studies have characterized exposure–response relationships as dynamic entities, changing in time.^{4,5} Such studies typically require larger amounts of data over a longer period of time, which is increasingly possible with larger clinical studies and electronic medical records. There is also a growing sophistication to statistical analysis. Shlipak *et al.*² used traditional survival analysis methods, accounting for changes in renal function over time with fixed-covariate values. Others have used time-dependent covariates,⁶ which can now be modeled for proportional hazards regression in most statistical software packages.⁷

Certainly, there are additional efforts required to characterize an exposure over time, yet the payoff for such efforts can be an improvement in our interpretation of evidence around exposure–disease relationships. With their study, Shlipak *et al.*² extend our mechanistic understanding of the kidney–cardiovascular relationship by acknowledging the importance of time and trajectory of kidney function decline. From an epidemiologic perspective, the Greek leader Pericles (perhaps, unknowingly) said it best: “Time may be the wisest counselor of all.”

DISCLOSURES

A.Y. was supported by a Doctoral Research Award from the Canadian Institutes of Health Research. A.X.G. was supported by a Clinician Scientist Award from the Canadian Institutes of Health Research.

REFERENCES

1. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006

2. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, Rifkin D, Sarnak MJ: Rapid decline of kidney function increases cardiovascular risk in the elderly. *J Am Soc Nephrol* 20: 2625–2630, 2009
3. Rothman K, Greenland S, Lash T: *Modern Epidemiology*, 3rd Ed, Philadelphia, Lippincott Williams & Wilkins, 2008
4. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, McAllister CJ, Budoff MJ, Salusky IB, Kopple JD: Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 70: 771–780, 2006
5. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 17: 1181–1191, 2006
6. Fisher LD, Lin DY: Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 20: 145–157, 1999
7. Thomas DC: Models for exposure-time-response relationships with applications to cancer epidemiology. *Annu Rev Public Health* 9: 451–482, 1988

See related article, “Rapid Decline of Kidney Function Increases Cardiovascular Risk in the Elderly,” on pages 2625–2630.

Aldosterone Blockade in Diabetic Nephropathy: Relative Risks and Potential Promise

Mario F. Rubin* and Raymond R. Townsend†

*Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; and †Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

J Am Soc Nephrol 20: 2487–2489, 2009.

doi: 10.1681/ASN.2009101036

In the 1950s, electrocortin, as aldosterone was then known,¹ was a relatively novel hormone, the importance of which in human pathophysiology was established by reports of cases of aldosterone excess by Conn in 1955.² Despite more than 50 yr of study, the breadth of many actions of aldosterone continues to unfold in basic, translational, and clinical milieus.

From a basic aspect, aldosterone has typical genomic effects. After receptor binding, aldosterone exposure initiates transcriptional processes, which increase protein synthesis in pathways that enhance sodium retrieval from tubular lumens, salivary and sweat glands, and colon. Nongenomic aspects have been reported in which aldosterone infusion reduces the caliber of isolated afferent and efferent arterioles³ through the activation of systems that inhibit endothelial nitric oxide action.⁴

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Mario F. Rubin, Massachusetts General Hospital, 165 Cambridge Street, Suite 302, Boston, MA 02114. Phone: 617-726-9023; Fax: 617-643-6722; E-mail: mfrubin@partners.org

Copyright © 2009 by the American Society of Nephrology