Am J Physiol Renal Physiol 311: F409–F410, 2016;
doi:10.1152/ajprenal.00317.2016.

Albumin: innocent bystander or culprit?

Anna J. Peired[1,2] and Markus Bitzer[3]

[1]*Excellence Centre for Research, Transfer and High Education for the Development of De Novo Therapies, Florence, Italy;* [2]*Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy; and* [3]*Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan*

Submitted 27 May 2016; accepted in final form 8 June 2016

ALPORT SYNDROME (AS) is a hereditary glomerulopathy associated with hearing loss and ocular abnormalities that, if left untreated, inevitably progresses to glomerulosclerosis and end-stage renal disease (ESRD) (6). AS is caused by mutations in collagen type IV genes and is associated with thickening and splitting of the glomerular basement membrane (GBM), ultimately rendering it leaky for albumin. Current treatment options for AS include angiotensin-converting enzyme inhibitors and other medications with antiproteinuric effects that are able to slow down disease progression. In particular, drugs administered before the onset of microalbuminuria successfully delay the progression to ESRD and increase life expectancy (3). Remission of albuminuria is associated with improved outcomes, and lowering albuminuria is a widely accepted treatment goal for AS and other glomerular diseases. However, the role of albumin beyond a disease marker has remained controversial because until recently there was no evidence that the improved patient outcome was a direct consequence of decreasing albuminuria. The study by Jarad et al. (4) in the *American Journal of Physiology-Renal Physiology* provides novel evidence suggesting that albumin participates in the progression of AS. To test the role of albumin in AS, the authors generated albumin knockout ($Alb^{-/-}$) mice and crossed them with an established in vivo model of AS, collagen (Col)4a3 knockout ($Col4a3^{-/-}$) mice. By comparing $Col4a3^{-/-}$ $Alb^{-/-}$ mice with $Col4a3^{-/-}$ mice, they elegantly demonstrated how the absence of albumin ameliorates inflammation, tubulointerstitial fibrosis, and glomerulosclerosis. These changes were associated with decreased transforming growth factor (TGF)-β signaling activity as well as reduced kidney injury molecule-1 and desmin expression.

It is important to note that $Alb^{-/-}$ mice do not exhibit a strong phenotype besides hyperlipidemia. It is even more intriguing that albumin deficiency has been observed in humans. Despite albumin being one of the most abundant protein in the bloodstream and decreased serum albumin levels being associated with the accumulation of extracellular fluid in disease states, albumin-deficient humans appear to survive to adulthood without obvious abnormalities but are not completely protected from glomerular disease. The findings reported here were recently confirmed in another study (8) and introduce $Alb^{-/-}$ mice as a new research tool for studies on albumin biology and its role in disease.

The observations presented by Jarad et al. (4) that $Col4a3^{-/-}$ $Alb^{-/-}$ mice show fewer globally sclerosed glomeruli and less tubulular interstitial fibrosis but similar numbers of segmentally sclerosed glomeruli suggests that albumin may rather be an accelerator than the initiator of the glomerular changes. On the other hand, GBM and podocyte structures as well as podocyte number were ameliorated in $Col4a3^{-/-}$ $Alb^{-/-}$ compared with $Col4a3^{-/-}$ Alb wild-type mice. The discoveries of human mutations as well as genetic studies in mice on the role of GBM components in AS from the authors and others support essential roles for the GBM in glomerular permselectivity and normal podocyte function (6, 9). This hypothesis postulates that the GBM limits the access of albumin to podocytes and Bowman's space and that defects in the GBM lead to albuminuria and increased exposure of podocytes to albumin. The findings of amelioration of glomerular damage in albumin-deficient mice could suggest that albumin alters the permselectivity of the GBM and thereby contributes to progressive GBM dysfunction. This may share some commonalities with extracellular nucleotides, which increase glomerular permeability to albumin by rearrangement of the podocyte actin cytoskeleton preceding increased urinary albumin excretion (5). Blockade of the renin-angiotensin system using angiotensin-converting enzyme inhibitors or angiotensin receptor blockers not only slows the progression of diabetic nephropathy and other glomerular disease but also reduces albuminuria. Furthermore, renin-angiotensin system blockade ameliorates podocyte damage and loss, which has recently also been described in patients with AS (10).

But how can lack of albumin ameliorate podocyte stress or damage? Lack of albumin may simply lead to decreased mechanical stress or albumin could interfere with sensing of GBM components by podocytes, which is already impaired in AS (3). In addition, albumin impairs retinoic acid (RA)-induced differentiation of renal progenitor cells into podocytes (7) by sequestering RA in a mouse model of focal segmental glomerulosclerosis. Treatment with RA reduced proteinuria and increased podocyte numbers. Moreover, podocyte stress can be promoted via free fatty acids bound to albumin (2). Furthermore, decreased TGF-β/Smad signaling has been detected in podocytes and tubular epithelial cells of $Col4a3^{-/-}$ $Alb^{-/-}$ mice, suggesting interference with TGF-β/Smad signaling, which promotes tubulointerstitial fibrosis and podocyte stress induced by albumin (1). Thus, albumin may be an extracellular amplifier of TGF-β signaling activity, but the underlying mechanisms remain to be determined.

This study suggests that during AS and possible other glomerular disorders, albumin represents not only a marker but also contributes to the progression of glomerular disease. The findings not only raise many very interesting questions but also provide a tool to experimentally test them and gain novel insights into the mechanistic role of circulating albumin in kidney disease, which may lead to novel therapeutic strategies to delay the progression of glomerular disease.

Address for reprint requests and other correspondence: A. J. Peired, Denothe Center, Univ. of Florence, Viale Pieraccini 6, Florence 50139, Italy (e-mail: anna_peired@hotmail.com).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

A.J.P. and M.B. drafted manuscript; A.J.P. and M.B. edited and revised manuscript; A.J.P. and M.B. approved final version of manuscript.

REFERENCES

1. **Abbate M, Zoja C, Morigi M, Rottoli D, Angioletti S, Tomasoni S, Zanchi C, Longaretti L, Donadelli R, Remuzzi G.** Transforming growth factor-beta1 is up-regulated by podocytes in response to excess intraglomerular passage of proteins: a central pathway in progressive glomerulosclerosis. *Am J Pathol* 161: 2179–2193, 2002.
2. **Chung JJ, Huber TB, Gödel M, Jarad G, Hartleben B, Kwoh C, Keil A, Karpitskiy A, Hu J, Huh CJ, Cella M, Gross RW, Miner JH, Shaw AS.** Albumin-associated free fatty acids induce macropinocytosis in podocytes. *J Clin Invest* 125: 2307–2316, 2015.
3. **Gross O, Perin L, Deltas C.** Alport syndrome from bench to bedside: the potential of current treatment beyond RAAS blockade and the horizon of future therapies. *Nephrol Dial Transplant* 29, *Suppl* 4: iv124–iv130, 2014.
4. **Jarad G, Knutsen RH, Mecham RP, Miner JH.** Albumin contributes to kidney disease progression in Alport syndrome. *Am J Physiol Renal Physiol* 311: F120–F130, 2016.
5. **Kasztan M, Piwkowska A, Kreft E, Rogacka D, Audzeyenka I, Szczepanska-Konkel M, Jankowski M.** Extracellular purines action on glomerular albumin permeability in isolated rat glomeruli; insights into the pathogenesis of albuminuria. *Am J Physiol Renal Physiol* 311: F103–F111, 2016.
6. **Kruegel J, Rubel D, Gross O.** Alport syndrome–insights from basic and clinical research. *Nat Rev Nephrol* 9: 170–178, 2013.
7. **Peired A, Angelotti ML, Ronconi E, la Marca G, Mazzinghi B, Sisti A, Lombardi D, Giocaliere E, Della Bona M, Villanelli F, Parente E, Ballerini L, Sagrinati C, Wanner N, Huber TB, Liapis H, Lazzeri E, Lasagni L, Romagnani P.** Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J Am Soc Nephrol* 24: 1756–1768, 2013.
8. **Roopenian DC, Low BE, Christianson GJ, Proetzel G, Sproule TJ, Wiles MV.** Albumin-deficient mouse models for studying metabolism of human albumin and pharmacokinetics of albumin-based drugs. *MAbs* 7: 344–351, 2015.
9. **Suh JH, Miner JH.** The glomerular basement membrane as a barrier to albumin. *Nat Rev Nephrol* 9: 470–477, 2013.
10. **Wickman L, Hodgin JB, Wang SQ, Afshinnia F, Kershaw D, Wiggins RC.** Podocyte depletion in thin GBM and Alport syndrome. *PLoS One* 11: e0155255, 2016.