CORRESPONDENCE

CD2AP, Dendrin, and Cathepsin L in the Kidney

Sanja Sever* and Jochen Reiser†

From the Division of Nephrology,* Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and the Department of Medicine,† Rush University Medical Center, Chicago, Illinois

To the Editor-in-Chief:

In the recent paper by Weins et al,¹ the authors examined role of dendrin with regard to kidney function. To do so, the authors crossed mice globally lacking adaptor protein CD2-associated protein (CD2AP) with mice globally lacking dendrin. Loss of dendrin resulted in delayed onset and severity of proteinuria and expanded the lifespan of mice lacking CD2AP.

We have previously shown that dendrin is a transcription factor that regulates expression of cytoplasmic cathepsin L (CatL) and that its relocalization from the membrane to the nucleus requires loss of CD2AP.² Furthermore, we and others have shown that appearance of cytoplasmic CatL leads to the loss of dynamin³ and synaptopodin⁴ due to proteolysis, which in turn results in reorganization of the actin cytoskeleton in podocytes.

Given previous studies as well as the data presented in Supplemental Figure S7,¹ we were surprised by the conclusions that “Cathepsin L is not expressed in podocytes in *Cd2ap*^{-/-} mice”^{1,p2152} and that “Cathepsin L in podocytes does not contribute to glomerular disease progression in *Cd2ap*^{-/-} mice.”^{1,p2153} Instead, the data clearly show that wild-type control littermates lack CatL-positive staining. Global loss of *Cd2ap* led to an increase in the level of CatL-positive staining at several distinct locations in the kidney. The most pronounced staining was detected in proximal tubules, whereas moderately positive signal was detected in the Bowman capsule as well as the podocytes. This CatL positive signal was completely abrogated in mice lacking both CD2AP and dendrin. Together, these data provide direct support for our original hypothesis that dendrin is a CatL transcription factor and that its ability to induce CatL expression requires loss of CD2AP.² Granted, overall CatL staining, although similar to our published results, is generally less pronounced.² Difference in signal intensity is most likely due to different antibodies used, since Weins et al¹ used commercially available anti-CatL antibody (Sigma Aldrich) whereas we used polyclonal antibody specifically raised to detect cytoplasmic CatL.² It is also

important to note that both cytoplasmic CatL and its downstream target GTPase dynamin are enzymes, and thus their physiological roles in any given cell, including podocytes, cannot be assigned based on the level of immunostaining.

Furthermore, although our original study used podocytes as the model system, CD2AP⁴ and possibly dendrin⁵ may be expressed in diverse cells of the kidney, including tubules. The data from Weins et al¹ suggest that dendrin–CD2AP-dependent regulation of CatL expression, originally identified in podocytes, is also present in other cells of the kidney including proximal tubules.⁵ Since both animal models are global knockdown models, not podocyte-specific knock-downs, it is puzzling that Weins et al¹ suggest that the observed effect of the loss of dendrin on the survival is solely driven by its effect in podocytes. Indeed, CatL-positive staining has been detected at identical distinct locations in kidneys of patients suffering from diabetic nephropathy including Bowman capsule, podocytes, and proximal tubules.³ It is well-established that injury to proximal and distal tubules plays a major role during disease progression of diabetic nephropathy.⁶ It is therefore reasonable to suggest that observed extension of survival in *Cd2ap*^{-/-} Dendrin^{-/-} animals could be explained by the global loss of dendrin in multiple types of kidney cells.

References

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Disclosures: S.S. and J.R. have pending and issued patents on novel strategies for kidney therapeutics and stand to gain royalties from their commercialization. They are also co-founders of TRISAQ Inc. (Miami, FL), a biotechnology company in which they have financial interest.

Address correspondence to Sanja Sever, Ph.D., Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; or Jochen Reiser, M.D., Ph.D., Department of Medicine, Rush University Medical Center, Chicago, IL 60612. E-mail: ssever@partners.org or jochen_reiser@rush.edu.

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