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COMMENT

Relations between glomerular hyperfiltration and podocyte injury: potential role of Piezo1 in the Rac1-mineralocorticoid receptor activation pathway

Yuichi Yoshida[1] · Hirotaka Shibata[1]

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Glomerular epithelial cells (podocytes) are highly differentiated cells that cover the glomerular basement membrane from the outside and serve as the final filtration barrier for blood proteins [1]. Several mechanisms have been reported for podocyte damage due to hypertension. Renal blood flow is reduced by atherosclerosis, which leads to increased renin activity and angiotensin II (Ang II) expression as a compensatory response. This increase in Ang II level results in inflammation, which leads to a decrease in podocyte number [2]. In addition, hyperfiltration in conditions such as hypertension with diabetes results in glomerular expansion due to increased blood flow, which causes mechanical stress on podocytes as the basement membrane is expanded, leading to podocyte loss [3].

Piezo proteins are ion channels, discovered in 2010 that are activated by mechanical stimuli [4]. These proteins are subunits that form the pores of ion channels, which open in response to mechanical stimuli to allow positively charged ions, including calcium, to enter the cell. Two Piezo proteins have been identified to date, Piezo1 and Piezo2, which are expressed mainly in non-sensory and sensory organs, respectively. Piezo1 is also known to be expressed in glomeruli and tubules, including podocytes, but its activities during podocyte injury when hypertensive glomerular damage develops remain unclear.

RAS-related C3 botulinum toxin substrate 1 (Rac1) enhances the transcriptional activating effect of mineralocorticoid receptor (MR) under conditions of dietary salt excess due to increased nuclear translocation of the MR [5]. That is, activated Rac1 increases salt sensitivity and blood pressure, as in primary aldosteronism.

Ogino et al. [6] showed that Piezo1 was overexpressed in podocytes, mesangial cells, and distal tubular cells in uninephrectomized, aldosterone-infused, salt-loaded mice, a hypertensive model of increased intraglomerular pressure, using RNAscope multiplex in situ hybridization assay. In a series of in vitro experiments, mechanical stretching of Piezo1-expressing cultured podocytes increased expression of activated Rac1 and podocyte injury markers, such as *plasminogen activator inhibitor-1* (*Pai1*), *serum/glucocorticoid regulated kinase 1* (*Sgk1*), and *Monocyte chemoattractant protein 1* (*Mcp1*), and these increases in marker levels were inhibited by GsMTx4, a Piezo1 antagonist. In summary, these observations indicated that the stress of glomerular basement membrane stretching due to increased intraglomerular pressure increases the expression of Piezo1 in podocytes, which in turn increases activated Rac1 and podocyte injury markers. In addition, MR antagonists (MRAs) and Rac inhibitors inhibit Piezo1 activation and attenuate the increases in podocyte injury markers (Fig. 1).

Ogino et al. [6] elucidated the pathophysiology of chronic kidney disease (CKD) resulting in hypertension that can lead to hyperfiltration of the renal glomeruli. This study is novel in that Piezo1 was induced by mechanical stretch stimulation and shown to be associated with the Rac1-MR activation pathway resulting in podocyte injury during glomerular hyperfiltration. Therefore, Piezo1 blockers have potential for treatment of CKD due to hypertension.

Although not indicated in all stages of disease, primary aldosteronism and obesity-related hypertension, as well as diabetic kidney disease, result in increased intraglomerular pressure, which causes basement membrane stretching and consequent podocyte damage. These diseases have been reported to complicate CKD in many cases, and it has been

✉ Hirotaka Shibata
hiro-405@cb3.so-net.ne.jp

[1] Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan

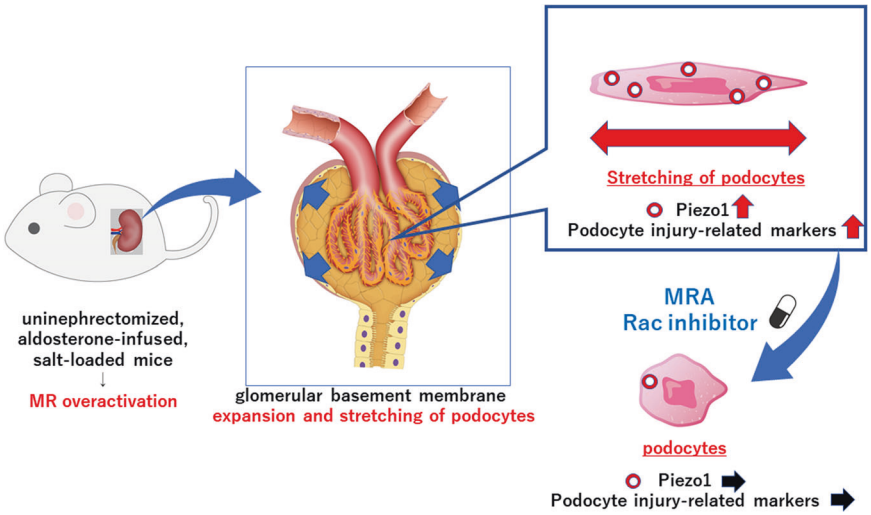

Fig. 1 Relations between podocytes, Peizo1, and MR. In hypertensive models of MR overactivation, renal glomeruli are distended, podocytes are stretched, Piezo1 is upregulated, and podocyte injury-related marker levels are elevated. Administration of MRA or Rac inhibitors inhibited these changes. MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; Rac, RAS-related C3 botulinum toxin substrate

speculated that podocyte injury may be one of the causes. The study by Ogino et al. [6] was the first to show that podocyte injury was caused by increased Piezo1 expression due to mechanical stretching and the resulting MR activation. Future clinical studies are expected to investigate whether podocyte injury actually occurs in patients with primary aldosteronism and obesity-related hypertension. In particular, MRAs are not currently the first-line treatment for obesity-related hypertension [7]. Future studies to understand more fully the relations between obesity-related hypertension and podocyte and MR activation may lead to the adoption of MRAs as the first-line treatment for this condition. Yoshida et al. [8] showed that the urinary albumin excretion rate (UACR) decreased in patients with primary aldosteronism treated with the MRA esaxerenone, in a manner independent of blood pressure reduction, but the mechanism of this UACR reduction was not clarified. The results of the in vivo study by Ogino et al. [6] demonstrated a decrease in systolic blood pressure with esaxerenone administration, but it was not possible to determine whether this was independent of improvement of podocyte injury because it was not evaluated. However, inhibition of MR activation with Rac inhibitors suppressed Piezo1 expression and decreased podocyte-related marker levels without lowering blood pressure, suggesting that inhibition of MR activation may reduce podocyte injury and thus protect the kidney. Therefore, it is possible that the inhibition of MR activity by esaxerenone for primary aldosteronism reported by Yoshida et al. [8] may have led to a reduction in UACR, independent of blood pressure, by directly suppressing podocyte injury.

This study had several limitations. First, the animal model consisted of uninephrectomized, aldosterone-infused, salt-loaded mice, a CKD model with elevated intraglomerular pressure. As noted above, hypertension is not necessarily associated with elevated intraglomerular pressure. In the case of nephrosclerosis due to atherosclerotic changes or other causes, blood flow to the glomeruli is reduced, a condition known as ischemic glomerulosclerosis. In this case, intraglomerular pressure does not increase. The role of Piezo1 in ischemic nephropathy should be clarified in future studies. Second, it remains to be determined whether MRAs and/or Rac inhibitors can inhibit all effects of Piezo1. Piezo1 is expressed in tubular cells in addition to podocytes, and its role in tubulointerstitial injury remains to be explored in future studies. Third, as noted above, diabetic kidney disease is similar to the model used in this study, but these differences should be examined because the effects on podocytes and Piezo1 may be different when urinary glucose is high, as compared to those under conditions of hypertension. Fourth, it will be interesting to determine how Piezo1 is altered when angiotensin-converting enzyme inhibitors or Ang II receptor antagonists and SGLT2 inhibitors are used to improve diabetic nephropathy because these drugs also decrease intraglomerular pressure. Fukuda et al. [3] reported the usefulness of podocin mRNA in the urine sediment as a marker of podocyte injury, and clarification of the relations between this biomarker and Piezo1 may be useful in clinical practice. Despite these limitations, the present study provided valuable insights into the relations between glomerular hyperfiltration and podocyte injury.

Compliance with ethical standards

Conflict of interest HS has honorarium from Daiichi-Sankyo Company, Bayer, Mochida Pharmaceuticals, Astrazeneca, Novartis Pharma, and Astellas. HS also received scholarship from Chugai and Bayer.

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