ANGIOTENSIN II (ANG II), acting on AT₁ receptors, results in a variety of physiological effects, such as vasoconstriction, tubular sodium retention, and increased arterial blood pressure (4, 5). Interestingly, increased ANG II signaling also results in increased urinary protein leakage. The increased protein leakage across the glomerular filtration barrier has classically been attributed to the hemodynamic effects of increased ANG II levels (2), and proteinuria is commonly used as a diagnostic marker for the progression of chronic kidney disease. Proteinuria is generally treated by targeting either ANG II production by administering angiotensin-converting enzyme inhibitors or directly interfering with AT₁ receptor signaling by administering angiotensin receptor blockers (3, 6). However, the pioneering study by Axelsson and co-workers (1) describes a novel mechanism by which ANG II directly and dynamically regulates “large pores” in the glomerular filtration barrier which causes increased protein leakage. Axelsson et al. isolated the effect of ANG II on filtration barrier permeability in vivo and could directly demonstrate that exogenously administered ANG II caused increased number of large pores independently of its hemodynamic effects. Furthermore, ANG II administration still caused an increased number of large pores even when concomitantly induced aldosterone signaling was blocked by spironolactone. Importantly, the ANG II-induced increase in large pores was reversible, further demonstrating a direct physiologically relevant role for ANG II in regulating the glomerular filtration barrier permeability to large macromolecules.

These findings have several clinically important implications. First, a novel mechanism for the regulation of protein permeability across the glomerular filtration barrier has been characterized, which may highlight new therapeutic strategies to treat proteinuric patients with developing chronic kidney disease. Second, the regulation of the glomerular filtration barrier is a dynamic process that can be reversed. However, it still remains to be determined whether changes induced in the filtration barrier by long-term exposure to increased ANG II levels are also reversible. Third, ANG II alone is a potent inducer of large pores in the filtration barrier.

So, how do we move forward from here? Perhaps the most urgent question is whether long-term exposure to ANG II causes similar changes to the filtration barrier, and if so, are these changes also reversible? The next important step is to elucidate the involvement of this novel mechanism in the commonly observed increased urinary protein leakage in experimental models of diabetes and hypertension, both common clinical conditions associated with increased proteinuria and increased risk to develop chronic kidney disease. The potential involvement of ANG II-induced oxidative stress should also be clarified. However, the intriguing idea of testing the concept of ANG II-regulated large pores in the corresponding patient populations, to finally establish its clinical relevance, remains a methodological challenge.

REFERENCES