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The influence of AT1R-mediated TRPC5 activation on podocytes

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The proper functioning of the human kidney filter depends inevitably on the integrity of highly specialized kidney cells, the podocytes. Over time their dysfunction reflected in foot process effacement and proteinuria commonly leads to progressive kidney disease. Focal segmental glomerulosclerosis, a disease histologically defined by podocyte loss, is the leading cause of end-stage renal disease with glomerular genesis.
Mutations in the calcium-permeable ion channels Transient Receptor Potential Canonical Channel 5 and 6 have been shown to cause focal segmental glomerulosclerosis imputing a major role to these channels in the course of disease pathogenesis.
Apart from that, the structural and functional integrity of podocytes relies on a balanced renin-angiotensin system. Experiments in rats using a transgenic overexpression of the Angiotensin II type 1 receptor showed podocyte-specific pathologies such as podocyte hypertrophy, proteinuria, and, eventually, focal segmental glomerulosclerosis. Previous data had established a link between angiotensin II signaling and subsequent activation of transient receptor potential canonical channel 5, suggesting the angiotensin receptor's involvement in podocyte injury.
To test this hypothesis and selectively investigate the role of the angiotensin II type 1 receptor in the pathogenesis of podocyte injury, we established a unique genetically altered receptor in podocytes that is constantly activated and does not get internalized. Secondly, we prevented calcium influx with the help of selective TRPC5-inhibitor ML204 to see if angiotensin II induced effects are, in fact, mediated by TRPC5 and, therefore, reversible.
Our results showed that podocytes expressing the constantly activated Angiotensin II receptor type 1 show impaired cell viability, higher ROS generation, and impaired mitochondrial integrity. The pharmacological inhibition of the transient receptor potential cation channel 5 partly reversed these pathological changes in a time-dependent manner, suggesting that the angiotensin II receptor type 1 is an upstream activator of TRPC5 and that both receptors are involved in the signaling pathway leading to podocyte death. By providing mechanistic insights into podocyte pathophysiology, we pave the way for new therapeutic targets.