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## **Mechanism of Podocyte Injury: CaSR and Actin-Cytoskeleton**

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Proteinuria has several causes, including both genetic disorders and acquired forms. The underlying cause of proteinuria is a disturbance in the size selectivity of the glomerular filtration barrier, which is extensively reliant on podocytes. A damaged podocyte architecture is one of the first indications of glomerular damage. The essential role of the actin cytoskeleton in the maintenance of functional podocyte structure has been unequivocally established. Podocyte foot processes, actin-based membrane extensions, contain two molecularly distinct areas that manage actin dynamics: a slit diaphragm and focal adhesions. Although the loss of the foot processes involves the degradation of the multiprotein complexes of the slit diaphragm, the focal adhesions are the sites where the stress is compensated by the forces generated by the actin-network. The crucial role of Ca<sup>2+</sup> homeostasis in regulating the podocyte cytoskeleton is well characterized. For example, gain-of-function mutations of the transient receptor potential channel 6 (TRPC6) calcium channel gene, which cause excessive entry of Ca<sup>2+</sup> into the podocyte cytoplasm, are associated with hereditary focal and segmental glomerular sclerosis.

Calcimimetics allosterically increase calcium ion sensitivity of the calcium receptor (CaSR). Using a CaSR knockdown in podocytes and a podocyte-specific CaSR knockout in mice, we uncovered a stabilizing role for the actin cytoskeleton and cell adhesion. We generated a CaSR knockdown in cultured mouse podocytes and a podocyte-specific CaSR knockout in BALB/c mice to investigate its role in proteinuria and renal function. Knockout of CaSR in podocytes abolished calcium ion flux mediated by the calcimimetic R-568, disrupted the actin cytoskeleton, and decreased cell attachment and migration speed. Short-term relief of albuminuria and proteinuria was observed in 4 children treated with cinacalcet. In my talk I will give some further details and a potential outlook on our findings