SIGNIFICANCE STATEMENT

Transient Receptor Potential channel C6 (TRPC6) is a nonspecific calcium (Ca^{2+})-conducting ion channel expressed at or near the slit diaphragm of the podocyte. TRPC6 gain-of-function mutations lead to hereditary FSGS, whereas acquired glomerular proteinuric diseases are associated with TRPC6 overexpression. This paper elucidates a novel mechanism that links TRPC6-mediated Ca^{2+} influx to calpain-1 activity and subsequent loss of Talin-1, which anchors the podocyte cytoskeleton to integrins, as well as calcineurin activation, thereby causing podocyte injury characteristic for FSGS and other podocytopathies. This identifies both TRPC6 and calpain-1 as future therapeutic targets in the treatment of proteinuria and prevention of glomerular injury, which was supported by showing a beneficial effect of the calpain inhibitor calpeptin in a rodent model of experimental FSGS.