

## **SIGNIFICANCE STATEMENT**

The structure and function of podocytes are dependent on an intricate actin cytoskeleton. Serum response factor (SRF) is a master regulator of the actin cytoskeleton; however, there is little information about SRF in podocyte biology. Podocyte-specific knockout of *Srf* in mice results in foot process effacement and renal failure, leading to early death. Combined genetic inactivation of the SRF cofactors *Mkl1/Mkl2* phenocopies the *Srf* knockout. Cultured podocytes with reduced SRF exhibit defects in the actin cytoskeleton and dysregulated expression of several genes, including those necessary for a functional actin cytoskeleton. SRF and MKL1/MKL2 are critical for podocyte structure and normal renal function. Future work should evaluate these factors in human renal disease and interrogate target genes essential for podocyte homeostasis.