SIGNIFICANCE STATEMENT

Secretion of the matrix crosslinking enzyme transglutaminase-2 (TG2) from tubular epithelial cells has been shown to contribute to fibrotic remodeling, a primary pathologic process in CKD. To discover the pathway for secretion of TG2, a comparative proteomic strategy was developed. Proteins that interact with TG2 were identified by TG2 immunoprecipitation from wild-type and TG2 knockout fibrotic kidney membranes followed by SWATH mass spectroscopy. The TG2 interactome was enriched in extracellular vesicle proteins, suggesting that TG2 is secreted in exosomes. Studies in cultured tubular epithelial cells support this conclusion and suggest that TG2 is a binding cargo of syndecan-4. The finding of TG2 in the urine of patients with CKD raises the possibility that block of vesicular TG2 could reduce TG2-driven matrix accumulation and diminish fibrosis.