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BAG2, a novel chaperone in renal fibrosis, acts to enhance TGF-β/smad3 binding in CKD patients.

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Objectives: The discovery of novel targets regulating TGF-β1 signaling is important for therapeutic development in kidney fibrosis. BAG2 (BCL2-related athanogene 2) is a type of chaperone protein that directs the correct folding of proteins and is known to be involved in cell fate decisions in several types of cancer. However, the regulatory mechanism of BAG2 in kidney fibrosis has not been studied.

Methods: We analyzed BAG2 expressions in data from the European Renal cDNA Bank (ERCB) and paraffinized kidney samples obtained from patients undergoing nephrectomy. We used NIH3T3 and HEK293 cells for western blot analysis, real-time PCR, or immunofluorescent analysis. CAGA luciferase assay and FACS analysis were performed. Kidney fibrosis was induced in unilateral ureteral obstruction and adenine diet WT or BAG2 knockout mice.

Results: The gene expression level of BAG2 was negatively correlated with eGFR (ERCB data). Immunohistochemical analysis confirmed higher intensity of BAG2 staining in kidneys from patients with chronic kidney disease (CKD) than in controls. BAG2 expression increased in mice fibroblast cells (NIH3T3) after treatment with TGF-β1 and increased fibrosis-associated proteins. Suppressed TGF-β/Smad3 signaling promoter (CAGA) activity was observed in BAG2-depleted NIH3T3 cells, whereas increased CAGA activity was observed in BAG2-overexpressing cells. Western Blot Analysis of Immunoprecipitation revealed that BAG2 directly interacts with TGF-β type 1 receptor and Smad3. Interestingly, increased BAG2 expression enhanced the interaction of TGF-β type 1 receptor with Smad3, whereas decreased BAG2 expression attenuated their interaction. Analysis of the two CKD mice models showed excessive increases in BAG2 expression in the interstitial regions of the kidneys with advanced fibrosis, but reduced fibrosis in the kidneys of BAG2 knockout mice.

Conclusions: Our results suggest that BAG2 plays an important regulator in kidney fibrosis and could be a target for potential therapeutic strategies to reduce kidney fibrosis.