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BCL2 associated athanogene 2 (BAG2) mediates kidney fibrosis through TGFb1 signaling pathway

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Objectives: Kidney fibrosis is characterized by an excessive accumulation of extracellular matrix components and the common manifestation of chronic kidney disease. BAG2 (BCL2 associated athanogene 2) is associated with cell fate determination in several types of cancers as a co-chaperon protein inducing accurate folding of proteins. In addition, it has been reported that BAG2 expression of cancer-associated fibroblasts promotes breast cancer metastasis. We designed this study to explore the roles of BAG2 during the pathogenesis of kidney fibrosis.

Methods: Mouse fibroblast cells (NIH3T3) were treated with TGFb1 to induce myofibroblast differentiation. NIH3T3 cells were transfected with BAG2 specific shRNA by using a lentivirus packaging vector according to the manufacturer's instructions. Cells stably expressing Myc-tagged BAG2 were generated by retrovirus infection. Bag2+/+ and Bag2-/- mice (8 weeks of age) were anesthetized and the left ureter was ligated for unilateral ureter obstruction models.

Results: BAG2 expression increased in a mouse fibroblast NIH3T3 cells after TGFb1 treatment accompanied with increment of fibrogenic protein expressions. Overexpression of BAG2 accelerated myofibroblast differentiation by increasing phosphorylation of Smad3, whereas loss of BAG2 inhibited phosphorylation of Smad3 culminating in reduced fibrogenic marker expressions in NIH3T3 cells after treatment with TGFb1. We observed that BAG2-downregulation suppressed TGFb1 induced Smad3 driven CAGA transcriptional activity, and vice versa. immunoprecipitation assay revealed that endogenous interaction between BAG2 and Smad3, as well as between BAG2 and TGFb receptor type I. Deletion of BAG2 (BAG2-/- mice) resulted in mitigated TGFb1 signaling and decreased collagen deposition in obstructed kidneys.

Conclusions: Our data indicate that BAG2 enhances TGF-b1 signaling pathway by activating Smad3 phosphorylation and interaction with Smad3 and TGFb receptor type I during kidney interstitial fibrosis. BAG2 proteins could be the new target of drugs for kidney fibrosis.