Mutations in polycystin-1 (PC1) lead to autosomal-dominant polycystic kidney disease (ADPKD), a leading cause of renal failure for which no treatment is available. PC1 is an integral membrane protein, which has been implicated in the regulation of multiple signaling pathways including the JAK/STAT pathway. Here we show that membrane-anchored PC1 activates STAT3 in a JAK2-dependent manner, leading to tyrosine phosphorylation and transcriptional activity. The C-terminal cytoplasmic tail of PC1 can undergo proteolytic cleavage and nuclear translocation. Tail-cleavage abolishes the ability of PC1 to directly activate STAT3 but the cleaved PC1 tail now coactivates STAT3 in a mechanism requiring STAT phosphorylation by cytokines or growth factors. This leads to an exaggerated cytokine response. Hence, PC1 can regulate STAT activity by a dual mechanism. In ADPKD kidneys PC1 tail fragments are overexpressed, including a unique ~15-kDa fragment (P15). STAT3 is strongly activated in cyst-lining epithelial cells in human ADPKD, and orthologous and nonorthologous polycystic mouse models. STAT3 is also activated in developing, postnatal kidneys but inactivated in adult kidneys. These results indicate that STAT3 signaling is regulated by PC1 and is a driving factor for renal epithelial proliferation during normal renal development and during cyst growth.