Mutations in polycystin-1 (PC1) give rise to autosomal-dominant polycystic kidney disease (ADPKD), a leading cause of renal failure without an available treatment. PC1, an integral membrane protein, is implicated in regulating various signaling pathways, including the JAK/STAT pathway. This study reveals that membrane-anchored PC1 activates STAT3 in a JAK2-dependent manner, resulting in tyrosine phosphorylation and transcriptional activity. The C-terminal cytoplasmic tail of PC1 can undergo proteolytic cleavage and nuclear translocation. Tail-cleavage eliminates PC1's direct activation of 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. Thus, PC1 can regulate STAT activity through a dual mechanism. In ADPKD kidneys, PC1 tail fragments, including a unique ~15-kDa fragment (P15), are overexpressed. STAT3 is robustly activated in cyst-lining epithelial cells in human ADPKD, as well as in orthologous and nonorthologous polycystic mouse models. While STAT3 is activated in developing and postnatal kidneys, it is inactivated in adult kidneys. These findings suggest that STAT3 signaling is regulated by PC1 and serves as a driving factor for renal epithelial proliferation during normal renal development and cyst growth.