Inhibition of the overactivated alternative complement pathway in autosomal dominant polycystic kidney disease (ADPKD) retards disease progression in animal models; however, it remains unknown how complement factor B (CFB) is upregulated in ADPKD. Here, we showed that the overexpression of CFB in cystic kidneys is associated with increased JAK2/STAT1 activity and enhanced expression of the polycystin-1 C-terminal tail (PC1-CTT). Overexpression or blockage of STAT1 increased or decreased CFB expression and CFB promoter activity. Moreover, overexpression of PC1-CTT induced JAK2/STAT1 activation and CFB upregulation in renal tubular epithelial cells. Furthermore, PC1-CTT overexpression increased human CFB promoter activity, whereas dominant negative STAT1 plasmids or mutation of putative STAT1 responsive elements decreased PC1-CTT-induced CFB promoter activity. The effect of CFB on macrophage differentiation was tested on a mouse macrophage cell line. Bioactive CFB dose dependently promoted macrophage M2 phenotype conversion. In addition, conditioned media from renal epithelial cells promoted macrophage M2 phenotype conversion which was blocked by STAT1 inhibition in a dose-dependent manner. Conditioned media from PC1-CTT-transfected renal epithelial cells further promoted macrophage M2 phenotype conversion, which was suppressed by fludarabine or a CFB antibody. In addition, we show that NF-kB acts downstream of PC1-CTT and may partly mediate PC1-CTT-induced CFB expression. In conclusion, our study reveals possible mechanisms of CFB upregulation in ADPKD and a novel role of PC1-CTT in ADPKD-associated inflammation. Furthermore, our study suggests that targeting STAT1 may be a new strategy to prevent inflammation in the kidney of patients with ADPKD.