In autosomal dominant polycystic kidney disease (ADPKD), the inhibition of the overactivated alternative complement pathway has been shown to retard disease progression in animal models. However, the mechanisms underlying the upregulation of complement factor B (CFB) in ADPKD remained unknown. This study unraveled the association between CFB overexpression in cystic kidneys and increased JAK2/STAT1 activity, coupled with enhanced expression of the polycystin-1 C-terminal tail (PC1-CTT). The research demonstrated that manipulating STAT1 levels could reciprocally modulate CFB expression and CFB promoter activity. Additionally, overexpression of PC1-CTT induced JAK2/STAT1 activation and upregulated CFB in renal tubular epithelial cells. Further experiments revealed that PC1-CTT overexpression increased human CFB promoter activity, and this effect was mediated through putative STAT1 responsive elements. The impact of CFB on macrophage differentiation was explored, showing that bioactive CFB promoted macrophage M2 phenotype conversion. Conditioned media from renal epithelial cells, particularly those overexpressing PC1-CTT, further facilitated macrophage M2 phenotype conversion, and this effect was suppressed by fludarabine or a CFB antibody. Moreover, the study identified NF-kB as acting downstream of PC1-CTT, partly mediating PC1-CTT-induced CFB expression. In conclusion, this study sheds light on the mechanisms of CFB upregulation in ADPKD, highlighting the novel role of PC1-CTT in ADPKD-associated inflammation. The findings also suggest that targeting STAT1 could be a promising strategy to mitigate inflammation in the kidneys of ADPKD patients.