

CD8⁺ T-cells play an important role in halting cystogenesis and provide a novel target for slowing ADPKD progression.

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INTRODUCTION	In cancer, a disease with many parallels to Autosomal Dominant Polycystic Kidney Disease (ADPKD), tumor progression not only involves epithelial signaling altered by oncogenic drivers, but also entails complex interactions between the cancer cell and the surrounding environment. For example, cancer cells can activate pathways that block the function of cytotoxic CD8 ⁺ T-cells, leading to immunoevasion and tumor progression. Inhibiting this pathway has given rise to novel FDA approved anti-cancer drugs. In ADPKD, therapeutic strategies, which focused primarily on targeting aberrations in renal epithelial cell signaling, have shown only modest success. Thus, repurposing therapeutic immunooncology agents from the cancer world to ADPKD is attractive. However, their potential to treat the disease is unclear, as we do not know the functional role of CD8 ⁺ T-cells in cystogenesis.
METHODS	Using flow cytometry, immunofluorescence, <i>in situ</i> staining, qPCR, histopathology, and antibody depletion, we evaluated the role of CD8 ⁺ T-cells and associated signaling pathways in cystogenesis using the homozygous ADPKD <i>Pkd1</i> p.R3277C (RC) model.
RESULTS	We observed increased numbers and activation of CD8 ⁺ T-cells in <i>Pkd1</i> RC kidneys correlating with disease severity compared to wildtype controls, and specific localization of these cells to cystic lesions. Furthermore, the CD8 ⁺ T-cell effector cytokine, interferon γ (IFN γ) was significantly increased in diseased kidneys as were the T-cell recruiting chemokines Cxcl9/Cxcl10. <i>In situ</i> hybridization showed that Cxcl9 was predominantly produced in cystic regions. Importantly, immunodepletion of CD8 ⁺ T-cells in <i>Pkd1</i> RC mice resulted in worsening of disease pathology compared to IgG-control, consistent with a protective role for CD8 ⁺ T-cells in cystogenesis. Additionally, we examined potential immunosuppressive mechanisms that would inhibit CD8 ⁺ T-cell function and found alterations in PD-1/PD-L1 immune-checkpoint proteins, increased numbers of regulatory T-cell numbers, and induction of the kynurenine pathway in this ADPKD model.
CONCLUSION	Our data indicates that CD8 ⁺ T-cells are upregulated, activated, and specifically recruited to cystic lesions in a murine model of ADPKD. Further, we show that they play a crucial role in attenuating cysts growth and that pathways aimed to interfere with their function are activated in ADPKD. Hence, therapeutic compounds designed to activate CD8 ⁺ T-cells may be promising novel ADPKD treatment options.