Blockade of IL-17A/IL-17RA interaction improves anti-PD-L1 therapy in ADPKD

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Introduction. Anti-interleukin (IL) -17A therapies has been approved for treatment in several inflammatory diseases. Howbeit, whether IL-17A and its receptor is a viable target in ADPKD has not yet been reported.

Methods. To validate the role of IL-17A in ADPKD, cyanidin, a flavonoid molecule, was administered that interrupted IL-17A/IL-17RA interaction in *Pkd1* mutant mouse models, including *Pkd1*$^{RC/RC}$ *and Pkd1*$^{fl/fl}$*:Pkhd1-Cre* mice. The molecular mechanisms involved in IL-17/IL-17RA signaling and cyanidin treatment were investigated with western blotting, qRT-PCR and siRNA analysis in *Pkd1* mutant renal epithelial cells and tissues. The interaction between IL-17RA and PD-L1 was determined with co-IP assay. The synergistic effect of cyanidin and PD-L1 antibody was investigated in *Pkd1*$^{RC/RC}$ mouse model.

Results. The expression of IL-17RA was increased in *Pkd1* mutant cells and kidneys. Blockade of IL-17A/IL-17RA interaction by cyanidin markedly delayed cyst growth and macrophage penetration via blunted activation of PKD signaling pathways and MCP-1 secretion through regulation of ACT1/TRAF6/SHP2 axis. Treatment with cyanidin also reduced TGF-β dependent fibrogenic response in *Pkd1* mutant kidneys. Interestingly, our study revealed that IL-17RA stabilized and regulated PD-L1 activity via its direct interaction. Conversely, inhibition of IL-17A/IL-17RA interaction reduced PD-L1 expression at the post-transcriptional level. Mechanistically, E3 ligase ACT1 monoubiquitinates PD-L1 leading to endocytic sorting and lysosomal degradation. In support of a synergistic therapy approach, we found that combination treatment using cyanidin and PD-L1 antibody exhibited significantly higher efficacy in *Pkd1* mutant kidneys. This approach further alleviated immunosuppression within the cystic microenvironment via increased accumulation of cytotoxic CD8+ T lymphocytes and cystic renal epithelial apoptosis in *Pkd1* mutant kidneys.

Conclusions. Targeting IL-17A/IL-17RA delays cyst growth in ADPKD mice, and this effect can be synergized with the co-treatment of PD-L1 antibody, most possibly mediated by the mechanism that IL-17A/IL-17RA leads to stabilization of PD-L1 and immune escape in ADPKD.

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