

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent potentially lethal monogenic disorder. Mutations in the *PKD1* gene, which encodes polycystin-1 (PC1), account for approximately 78% of cases. PC1 is a large 462-kDa protein that undergoes cleavage in its N and C-terminal domains. C-terminal cleavage produces fragments that translocate to mitochondria. We show that transgenic expression of a protein corresponding to the final 200 amino acid (aa) residues of PC1 in two *Pkd1*-KO orthologous murine models of ADPKD suppresses cystic phenotype and preserves renal function. This suppression depends upon an interaction between the C-terminal tail of PC1 and the mitochondrial enzyme Nicotinamide Nucleotide Transhydrogenase (NNT). This interaction modulates tubular/cyst cell proliferation, the metabolic profile, mitochondrial function, and the redox state. Together, these results suggest that a short fragment of PC1 is sufficient to suppress cystic phenotype and open the door to the exploration of gene therapy strategies for ADPKD.