Autosomal dominant polycystic kidney disease (ADPKD) stands out as the most prevalent potentially lethal monogenic disorder. The majority of cases, approximately 78%, result from mutations in the PKD1 gene, responsible for encoding polycystin-1 (PC1). PC1, a sizable 462-kDa protein, undergoes cleavage in both its N and C-terminal domains. Notably, C-terminal cleavage yields fragments that translocate to mitochondria. In this study, transgenic expression of a protein corresponding to the final 200 amino acid (aa) residues of PC1 is demonstrated to suppress the cystic phenotype and preserve renal function in two Pkd1-KO orthologous murine models of ADPKD. This suppression is contingent upon an interaction between the C-terminal tail of PC1 and the mitochondrial enzyme Nicotinamide Nucleotide Transhydrogenase (NNT). The interaction plays a crucial role in modulating tubular/cyst cell proliferation, the metabolic profile, mitochondrial function, and the redox state. Collectively, these findings suggest that a short fragment of PC1 holds the potential to effectively suppress the cystic phenotype, opening avenues for exploring gene therapy strategies for ADPKD.