Enhanced Protein Folding via XBP1 Activation Ameliorates ADPKD Due to PC1 Misfolding

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Background

Pkd1 is one of the two genes responsible for autosomal dominant polycystic kidney disease (ADPKD). In ADPKD, ~30% of mutations are missense predicted to result in reduced PC1 function. *XBP1* encodes the main chaperone modulator of the ER unfolded protein response. Here we investigated the role of XBP1 as a “genetic” chaperone therapy which may affect the levels of functional PC1 carrying patient derived missense mutations using the p.R2220W human REJ mutant (p.R2216W in mouse) as a representative candidate.

Methods

The effect of XBP1 on the expression and trafficking of the PC1-R2220W-V5 mutant was determined *in vitro*. A *Pkd1*^{R2216W} knock-in mouse model was generated. Using this backbone, *Pkd1*$^{R2216W/fl}$*;Pkhd1-Cre* and *Pkd1*$^{R2216W/fl}$*;Pkhd1-Cre;XBP1-Rosa-floxstop-TG* mice were examined by morphological, functional and biochemical analyses.

Results

Expression of XBP1 in transiently cells expressing PC1-R2220W-V5 leads to increased expression and GPS cleavage of the mutant protein. Ciliary trafficking of PC1-R2220W was markedly improved by co-expression of XBP1 as compared with PC1-R2220W alone. At P16, *Pkd1*$^{R2216W/fl}$*;Pkhd1-Cre* mice developed cystic disease compared with *Pkd1*$^{R2220W/+}$

animals as seen via a significant increase in renal parameters [KW/BW, 0.01±0.001 vs. 0.13±0.008, ****p<0.0001; BUN, 33.35±4.44 vs. 102.2±26.4, **p=0.0042; n=10, 7]. Expression of the conditional XBP1 transgene in *Pkd1*$^{R2216W/fl}$*;XBP1-TG;Pkhd1-Cre* mice at P16 led to a significant decrease in the cystic burden compared to the controls [KW/BW, 0.07±0.006 vs. 0.13±0.008, ****p<0.0001; BUN 50.57±8.47 vs. 102.2±26.49, *p=0.027, n=10, 7]. Using TUNEL and Ki67 assays we found that induction of XBP1 in the cyst lining cells led to a significant reduction in proliferation with no impact on apoptosis suggesting that the improved cystic phenotype in the *Pkd1*$^{R2216W/fl}$*;XBP1-TG;Pkhd1-Cre* animals is due to a reduction in cyst growth.

Conclusion

Our data raises the possibility that *in vivo* chaperone therapy for the treatment of ADPKD may have a beneficial role for a subset of PC1 missense mutations.