Polycystin levels regulate cell death-survival response during nutrient starvation

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common cystic kidney disease, caused by mutations in either *PKD1* or *PKD2*, encoding for polycystin-1 (PC1) or polycystin-2 (PC2), respectively. The mechanism of cyst formation remains unknown. Renal ischemic injury or nephrotoxicity was proposed to enhance cystogenesis and explain the phenotypic variety between ADPKD patients. We therefore aimed to investigate the cellular response towards nutritional stress in mouse inner medullary collecting duct cells (IMCDs), either wild-type (WT) or lacking PC1 or PC2 (PC1 KO or PC2 KO), with a focus on cell survival (autophagy) and cell death (apoptosis).

METHODS

Autophagy was measured by assessing the number of autophagic vesicles (autophagosomes) using the autophagosome marker LC3-II and apoptosis was assessed by the levels of cleaved Caspase 3.

RESULTS

Basal autophagy appeared higher in mouse PC1 KO *versus* WT IMCDs. In contrast, PC2KO IMCDs displayed reduced basal autophagy and an abolished autophagic response towards 3h nutrient starvation. However, after prolonged (48h) nutrient starvation, autophagy levels were higher in both PC1 KO and PC2 KO IMCDs compared to WT IMCDs. This was associated with less apoptosis after 72h of nutrient starvation and increased cell death resistance in PC1 KO and PC2 KO compared to WT IMCDs. Interestingly, PC1 levels increased, while PC2 levels reduced upon nutrient starvation in WT, but not in PC2 KO and PC1 KO IMCDs, respectively.

CONCLUSIONS

Our data suggest that PC1 and PC2 interdependently regulate each other's levels under nutrient starvation. This determines the cell death *versus* survival response during nutritional stress, in which PC1 favors a pro-apoptotic and PC2 a pro-autophagic response. We conclude that cells lacking functional PC1 or PC2 have an aberrant stress-induced regulation of PC1 and PC2 levels resulting in more cell survival during nutrient starvation than WT cells.