Reviewer's report

Title: p21 is decreased in polycystic kidney disease and leads to increased epithelial cell cycle progression: Roscovitine reverses this effect

Version: 1 Date: 28 May 2007

Reviewer: Albert C.M. Ong

Reviewer's report:

General

This paper addresses the role of the cyclin-dependent kinase inhibitor p21 in PKD pathogenesis. The role of cyclins and CDKIs has been given prominence by the finding that the cyclin inhibitor roscovitine can arrest cyst progression in two other murine models of PKD (Bukanov et al, Nature 2006). The authors use 2 main models to investigate this link ie Han:SPRD rats and MDCK cells (HGF stimulation and p21 antisense). The pattern of p21 staining in human ADPKD tissue is reported.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Althought interesting, this study would benefit from further experimental support for their conclusions.

1. The pictures in Fig 2 are of insufficient resolution to determine segment or cellular localisation of p21. What was the pattern of p21 staining in female patients and in female Cy/+ rats? It is also surprising to find fairly uniform p21 staining in all nephron segments in the normal tissue.

2. Ideally, quantitative alterations in the level of p21 in human ADPKD tissues should be shown by immunoblotting. It was unclear to me as to how consistent the immunostaining data was considering there were 11 PKD kidneys and 5 normal controls. Perhaps this could be quantified in terms of % of p21 positivity or negativity in cysts/tubules.

3. The lack of any change in p21 in female Cy/+ rats despite cystic change is surprising and needs explanation. Perhaps this is telling us that p21 changes are not esssential in the cystic pathway in this model. Do the authors have any data on changes in cyclin activity or other CDKI in female mice?

4. The changes with HGF compared to control in Fig 4 need to be quantified. The term 'QM' is not explained (Quiescent media). There are actually two bands in Fig 4 which are labelled by the p21 antibody. What do these signify?

5. The antisense blots in Fig 5 do not show convincing knockdown of p21 levels in a dose-dependent manner. If 3 experiemnts have been done, then this should be quantified by densitometry.

6. In Fig 6, the 200nM AS (antisense) is reported in the legend to have a p value of 0.095 wrt the 200nM SC (sense) for thymidine incorporation. Is this correct?

7. Although the 400 nM AS lane is significantly different from the 400 nM SC, it is incorrect to state that the levels of p21 correlate inversely with thymidine uptake (page 13 para 3) - compare Figs 5 and 6.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'