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: 1 June 2007

Reviewer: Benjamin Cowley, Jr

Reviewer's report:

General

1) Is the question posed by the authors new and well described?
   Yes

2) Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Yes

3) Are the data sound and well controlled?
   Yes

4) Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5) Are the discussion and conclusions well balance and adequately supported by the data?
   Yes, except as noted in the comments for authors.

6) Do the title and abstract accurately convey what has been found?
   Yes

7) Is the writing acceptable?
   Yes, except for minor grammatical and stylistic issues.

Comments for authors

Numerous data have supported the concept that increased epithelial cell proliferation is an important pathophysiologic component of PKD. P21 is key regular of cell proliferation in a number of cell systems. The authors present data to suggest that p21 levels are decreased in human ADPKD and the Han:SPRD rat model of ADPKD. Furthermore, they present data showing that the cancer chemotherapeutic agent roscovitine increases p21 levels in Han:SPRD Cy/+ rats, and that this coincides with decreased renal epithelial cell proliferation and amelioration of cystic disease.

The studies are logical conceived and well described. Methods are adequately described. Data are clearly presented and are convincing, for the most part. Conclusions are supported by the data presented. The studies complement another report, which is appropriately referenced by the authors of this manuscript, of a beneficial effect of roscovitine in another rodent model of PKD. Enthusiasm for this report would be enhanced by addressing selected minor issues:

-------------------------------------------------------------------------------
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
None.
-------------------------------------------------------------------------------

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
In noncystic control male rats, p21 staining was evident in the glomeruli as well as the tubulointerstitial compartment (Fig. 2, top left). However, in cystic males, staining was much less intense, particularly in the tubulointerstitial compartment (Fig. 2, bottom left).

At low magnification, this looks to be correct, but the resolution of the figures is such that at higher magnification, it is difficult to definitively identify p21 staining in non-cystic animals in the tubulointerstitial compartment. It is difficult to exclude the possibility that p21 staining is localized to tubular epithelial cells in normal animals and that there is limited p21 staining in the tubulointerstitial compartment. Thus, the lessened p21 staining in cystic animals could be due to expansion of the tubulointerstitial compartment, which does not express p21. It is thought that this is a limitation of the resolution of the figures uploaded, and that higher resolution figures would resolve this issue. The authors may want to consult with the BioMed Central staff regarding the best way to upload high resolution figures.

Figure 4
Was there a 0 ng/ml control? I presume that the HGF was added by removing the serum free media and replacing it with media containing HGF at the concentrations indicated. A control for the media change using media with 0 ng/ml HGF would be useful; though I seriously doubt that this is simply an artifact of the media change, a 0 ng/ml HGF control would eliminate this possibility. Based on the legend for figure 7, “QM” (“quiescent media?”) may represent this appropriate control. If so, it should be stated in the legend for figure 4.

----------------------------------------------------------------------------------
Discretionary Revisions (which the author can choose to ignore)

Abstract, 1st sentence
Suggest “...(ADPKD) is a common genetic disease with few treatment options other than renal replacement...” read instead “...(ADPKD) is a common genetic disease with few treatment options other than renal replacement...”

Results, 2nd sentence and other locations throughout the manuscript
“In addition, hepatocyte growth factor, which comprises the “molecular switch” from cyst to tubule...”
This implies that HGF is the only mediator to induce the transition from cyst to tubule in culture. This is probably exaggerating.
Suggest instead: “In addition, HGF, which induces a transition from a cystic phenotype to a tubular phenotype, increases p21 levels. Furthermore, attenuation of p21 results in augmentation of cell cycle transit in vitro. Thus levels of p21 are inversely correlated with renal tubular epithelial cell proliferation.”

Results, Page 12
Suggest “Thus, p21 is downstream of HGF and likely mediates its function in maintaining the tubular (and hence non-cystic) phenotype...” read instead “Thus, p21 is downstream of HGF and may mediate its function in maintaining the tubular (and hence non-cystic) phenotype...”

Figure 3
Very nice.

What next?: Accept after minor essential revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

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

Declaration of competing interests:
I have received grant funding from Roche for studies of ADPKD.