Reviewer's report

Title: 3-Phosphoinositide-dependent Protein Kinase-1 (PDK1) Promotes Invasion and Activation of Matrix Metalloproteinases

Version: 2 Date: 14 March 2006

Reviewer: James Woodgett

Reviewer's report:

General
This is a revised version of the manuscript. I still disagree on a few semantic points, but it is at the discretion of the authors whether to address these.

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)
None

Discretionary Revisions (which the author can choose to ignore)

Point 3. On page 15: "To obtain a broader perspective of the significance of PDK1 activation in invasive breast cancer, tissue microarrays of node-negative, node-positive and metastatic breast cancer specimens were assessed for expression of pSer241PDK1 by IHC (Fig. 6B,C)."

It is not at all clear that S241 is a measure of activity as claimed. While autophosphorylation may be essential for activity, this site apparently does not change under any circumstances (for example it is not PI3K dependent whereas phosphorylation of Akt at T308 is). Instead, phospho-241 appears to mirror the expression level of PDK1. The authors could exchange the word "activation" to "expression" unless they have evidence that phosphorylation of this site does not correlate with level of expression.

While I agree that using different antibodies, etc, makes direct comparison difficult (there have been other tissue microarray data onAkt activation - e.g Sandra Dunn's work), PDK1 activity might be expected to correlate better with Akt activation since the former is the only known positive regulator of T308. That said, I realise its also possible there is an Akt phosphatase that opposes PDK1 activation and obfuscates the correlation.

Point 4. I perhaps wasn't clear on this point about correlations. I was getting at whether the authors were aware of evidence that PDK1 is amplified or mutationally activated in breast cancer. Is PDK1 a driver or a component that is consequentially activated by other genetic changes (in PI3K, PTEN, etc)? Whether it is a driver or not is irrelevant from the perspective of the potential for PDK1 inhibitors as possible therapeutic strategies, but relates instead to primary breast cancer and mechanisms of transformation. As the authors state in the Abstract, PDK1 is an effector but I find it...
interesting that it has yet (AFAIK) to be shown to be mutationally activated/amplified in human cancers.

**What next?:** Accept after discretionary 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

**Declaration of competing interests:**

I declare that I have no competing interests.