Reviewer’s report

Title: A Novel Oncolytic Adenovirus Targeting Cyclin E Overexpression Repressed Lung Tumor Growth

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Reviewer: Sarah Freemantle

Reviewer’s report:

In the manuscript “A Novel Oncolytic Adenovirus Targeting Cyclin E Overexpression Repressed Lung Tumor Growth” by Cheng et al the authors describe the development of a murine model to test the oncolytic ability of adenoviral therapies. They use an adenovirus that has the human cyclin E promoter driving an intact E1A expression cassette to preferentially allow viral replication in cyclin E overexpressing cells.

Major points:

The murine lung cancer cell line used was generated by overexpressing the cyclin E gene specifically in lung cells by putting it under the control of the lung specific surfactant protein C (SPC) promoter. Overexpression of cyclin E is thought to increase the activity of the cyclin E promoter through effects on the retinoblastoma protein. By using a mouse cell line, tumor studies in mice could be performed with immunocompetent mice allowing a more representative evaluation of this type of treatment in animals with a functional immune system.

Because of the nature of the virus containing the cyclin E promoter and the ED-1 cells containing a human cyclin E gene under the control of the SPC promoter there were some parts of this paper that became very confusing. The level of SPC promoter activity in cell lines is very low as expression of SPC is inhibited in cultured cells presumably because surfactant protein expression is growth restrictive. This is a consistent finding using transgenic models with the SPC promoter. To restore SPC promoter activity, cells need to be grown in 3D culture or reintroduced into animals. In the supplemental figure S1 while they could detect some human cyclin E expression through PCR I am not sure that the cyclin E protein shown there is human. How do they know it isn’t murine cyclin E protein?

It would help if the authors could clearly explain why overexpressed human cyclin E in these cells would make them more permissive to oncolytic adenovirus replication. It's quite possible that the cell line has compensated with excess murine cyclin E expressing to maintain that high growth rate and ability to grow in low to absent serum conditions.

The murine tumors had an unusual phenotype in that hexon viral protein encapsulated cells isolating them from adjacent cells and also isolating the virus. Has something like this been seen before and if not does this impact the
enthusiasm for this model?

Minor points:
Figure 5 has panels A-C and then panel B has a-d. This gets a little confusing. Make a-d panels, 1-4 or i-iv.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests