Reviewer's report

Title: Bcl11b mutations identified in murine lymphomas increase the proliferation rate of hematopoietic progenitor cells

Version: 3 Date: 22 June 2007

Reviewer: Martin Dyer

Reviewer's report:

To reiterate, the MS reports the occurrence of mutations in Bcl11b in a subpopulation of chemically-induced mouse T-cell lymphoma raising (again!) the suggestion that Bcl11b is a possible tumor suppressor gene (TSG).

However, these data are not really consistent with either the Bcl11b knockout mouse data (which show a differentiation block) or human data (where high level expression is frequently seen in T-cell precursor ALL – as seen in Jurkat cell line). The mutants described here might therefore have “gain of function” attributes. In this regard it is interesting to note that all the mutations occurred in cases with retention of the other allele of Bcl11b, indicating that this gene does not behave as a classical TSG ie loss of one allele and mutation of the other.

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

Taken together, I do not think that the data on Bcl11b are consistent with a simple TSG model, as proposed here. I think a more careful analysis of the described mutants is warranted. That is:-

a) Mutant Bcl11b must be shown to be dominant over wild-type – cotransfection of the mutants with wild-type Bcl11b must be performed.

b) Assessment on proliferation of effects on a wider panel of cell lines rather than just FDC-P1 – for example, derived T-cell lines with and possibly without Bcl11b expression. Might also be of interest to assess effects on B-cell lines!! Given the high degree of conservation of mouse and human genes, it might be possible to use human rather than mouse cell lines.

c) Assessment of expression of Bcl11b mutants on ability to induce any features of T-cell differentiation.

In short, I do not think the case for Bcl11b being a TSG has been adequately made. The experiments reported here are of some interest but are preliminary and need to be supported by additional data.

Apologies again for the delay in reply.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Minor points.

1. Abstract line 4: Bcl11b should be in italics
2. Page 3 penultimate line – BCL11B shows 88% identity to the mouse gene – at protein or nucleotide level? Please clarify.
3. Why are there two bands in the western of the Jurkat cell line with the BCL11B antibody?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Quality of written English: Acceptable

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