Reviewer’s report

Title: Bortezomib prevents cytarabine resistance in MCL, which is characterized by downregulation of dCK and up-regulation of SPIB resulting in high NF-κB activity

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Reviewer: Shannon Buckley

Reviewer's report:
Cytarabine-resistant MCL is characterized by down-regulation of dCK and up-regulation of SPIB resulting in high NF-KB activity

Freiburghaus, et. al. derived cytarabine resistant MCL cell lines and investigated alterations in resistant lines. Here the authors found that in cytarabine resistant cell lines deoxycytodine kinase (dCK) was down-regulated at the protein level and led to resistance of other nucleoside analogs. In addition they found that NF-KB pathway was increased in resistant lines. Overall, the manuscript is interesting however it was previously shown by other groups that resistant MCL cell lines down-regulate dCK and lead to cross resistance of nucleoside analogs limiting the novelty of the findings. There are a couple of points that would benefit from clarification.

Specific comments:

1) The manuscript title does not represent that key findings of the manuscript, and instead stresses down-regulation of dCK, which is already known. Editing the title would help the reader pinpoint the key findings in the manuscript.

2) Although the authors say in the text that dCK down-regulation was seen in three parallel experiments, the manuscript would benefit from seeing western blots for multiple resistant clones derived. Also, it is unclear the number of resistant clones analyzed and generated for both biological and technical replicates.

3) Does knockdown of NF-kB or SPIB in resistant cell lines alter cytarabine sensitivity?
4) In Figure 11; the authors include findings from patient samples, however the significance of this data is unclear do to being diagnostic samples. The authors present that patients have high level dCK at diagnosis, however it is unclear if relapse or resistant patients have altered dCK expression. In patients that are resistant to cytarabine or in relapse, do they express lower levels of dCK?

5) It is unclear whether the data represented in the gene expression analysis is technical or biologic replicates?

6) A number of figures lack error bars, and it is unclear whether these experiments were repeated. ie; figures 1, 5, 6 and 8.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.
Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.
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