Reviewer's report

Title: SUMOylation of sPRDM16 promotes leukemogenesis in acute myeloid leukemia

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Reviewer: Miroslawa Siatecka

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Major Compulsory Revisions

The manuscript by Dong et al. focuses on involvement of SUMOylation of sPRDM16 in stimulation of acute myeloid leukemia formation. The authors described the consequences of overexpression of sPRDM16 WT or SUMO deficient mutant sPRDM16 K568R in THP-1 cells that were differentiated upon PMA treatment. Based on the presented analyses the authors concluded that the presence of sPRDM16 WT leaded to better proliferation and self-renewal as compare to the control, the THP-1 cells alone or cells expressing sPRDM16 K568R. At the same time, the cell line with sPRDM16 WT showed impaired differentiation as monitored by the monocyte differentiation surface marker CD11b and level of cell adherence, when compared to non-SUMOyable mutant sPRDM16 K568R (CD11b+ : 45,5 % for sPRDM16 WT vs. 54,6% for sPRDM16 K568R). Excessive proliferation and impaired differentiation of cells are attributes of cancer formation. The idea of involvement of SUMOylation of proteins in leukemogenesis is not new. Nishikata et al [Oncogene (2011) 30, 4194–4207] published similar remarks regarding the same protein MELS1 (known also as sPRDM16), only different cell line was used. In addition, the manuscript contains the entire section of RESULTS devoted to repeating the results regarding the SUMOylation of sPRDM16, it includes the confirmation of the SUMO acceptor site, K568 as well, the data which were already published by Nishikata et al.

However, the strength of this manuscript is the study conducted directly in mice. The authors performed transplantation of GFP labeled THP-1 cells infected with lentiviruses carrying sPRDM16 WT or sPRDM16 K568R and analyzed the bone marrow as well as peripheral blood. The tissues containing sPRDM16 WT showed stronger engraftment of leukemic cells (GFP+) into both: bone marrow and peripheral blood, as compare to non-SUMOyable sPRDM16 K568R mutant. These analyses could be expanded and show the influence of the particular forms of sPRDM16 on morphology of blood cells etc.

In order to find a possible molecular mechanism underlying the different effects of overexpressed WT and SUMO deficient mutant of sPRDM16 K568R on THP-1 cells, the authors performed mRNA-seq analysis. Both cell lines showed distinct gene expression profile when the cells were treated with PMA. 237 genes were differentially expressed between sPRDM16 WT and sPRDM16 K568R. In my opinion these data require more comprehensive analysis and conclusions regarding leukemogenesis.
In general, my impression is that the manuscript was written in great haste, and therefore contains some inaccuracies:

- Line 35 - important references are not provided at the end of the paragraph
- annotations of several references are not complete: No. 2, No. 5 and No. 7
- Line 232 - the protein name is not correct: “Sharp-1” instead of “sPRDM16”
- not consistent writing “SUMOylation” or “sumoylation” throughout the manuscript
- not precise terms like “the growth of leukemia”
- not clear statements and conclusions- e.g. line 59: “We found that SUMOylation of sPRDM16 regulated the expression of genes during AML cell differentiation, and promoted the growth of leukemia while inhibiting cellular differentiation”
- in general, the text requires English corrections e.g. line 256: “simulation” instead of “stimulation”

In addition, the quality of the pictures 1C and 3A is poor and has to be improved.

Recommendation: Major revision - the authors should expand the sections containing data obtained from transplanted mice and analysis of RNA-seq data could be discussed in greater details.

I would recommend to check and correct English by a native speaker before possible publication.

Accept After Revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

'I declare that I have no competing interests'