Reviewer's report

Title: NK-like homeodomain proteins activate NOTCH3-signaling in leukemic T-cells

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Reviewer: Isabella Screpanti

Reviewer's report:

This manuscript by Nagel and colleagues contains interesting findings that postulate a novel pathogenic pathway in leukemogenesis for MSX2, a member of the NKL family. The experiments conducted on both primary T and tumor cells, as well as on several T-ALL cell lines, suggest that MSX2 is implicated via regulation of Notch3-signaling in both early T-cell differentiation and leukemogenesis. The experimental work is well thought and clearly presented. However, some issues need to be addressed.

Major Compulsory Revisions

1. Figure 1. The authors claim that MSX2 has a physiological role in T cell development. The data by realtime PCR in CD34+ vs CD3+ primary cells support this claim, suggesting that MSX2 is downregulated during T cell differentiation. However, it would be important to include the expression of MSX2 protein in CD34+ vs CD3+ cells in the Western blot analysis of panel 1B.

2. The authors do not perform sufficient controls to prove that Notch3 is either a direct or indirect target of MSX2.

3. Figure 4. The data of Notch3 expression in T-ALL cells seem to present high standard deviations. Are the observed differences statistically significant?

Discretionary Revisions

4. Figure 1E. Could the authors show Western blotting using Notch3 antibodies to compare Notch3 expression with MSX2 expression?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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