Review of: "Telomere transcription in MLL-rearranged acute leukemia: increased levels of TERRA associate with lymphoid lineage and are independent of telomere length and ploidy"

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TERRA (telomeric repeat-containing RNA) belongs to the group of long non-coding RNAs that exerts protection of telomeres, and consequently are part of the mechanisms that maintain genome stability. Despite being known that the transcriptional regulator mixed-lineage leukemia (MLL) associates to telomeres and regulate TERRA transcription, particularly important in response to telomere dysfunction, it is still unknown whether MLL-fusion proteins, the resultant of *MLL* rearrangements in leukemia, are also affecting TERRAs transcription. This is relevant since chromosomal rearrangements of MLL gene are found in aggressive leukemias in children and adults and is associated with a relatively poor prognosis despite improved treatment options. MLL encodes a methyltransferase that binds DNA and actives transcription of its target genes, *i.e.*, homeobox genes. In the present study it is shown that TERRA levels are higher in *MLL*-r acute lymphoblastic leukemia (ALL) cell lines compared to myeloid and non*MLL*-r ALL. This difference is not due to differences in telomere length and cell ploidy rather than a potential deregulated telomere transcription. The authors suggest that the high levels of TERRA associated to MLL-r present in lymphoid lineage correlates with marked genomic stability previously reported in pediatric *MLL*-r ALL.

There are some comments about this study:

1. Many results showed in figure 1 (panels A and C) were already published in a previous paper (Caslini C*et al.*, Mol Cell Biol 2009;29:4519–26) where it was shown for the first time the binding of MLL and MLL-r to telomeres and centromeres. New data was in panel D where the authors showed that in a non-MLL-r AML cell line (U-937) as well as in MLL-r ALL cell lines (ALL-PO and RS4;11) have similar telomerase activity. It would be expected that the authors tested telomerase activity in lymphoid cells with non-MLL-r and tested whether ectopic MLL-AF4 and/or -AF9 fusion proteins may modify telomerase activity. Otherwise, the authors did not present enough data to establish a relationship between the MLL-r with the telomerase activity.
2. The graph in panel B of figure 2 is very difficult to follow, there are myeloid and lymphoid cell lines without or with MLL-r. It would be better to separate the data and make it easier the interpretation.
3. No correlation was found between MLL-r and -non-r with respect to telomere length in the cell lines analyzed. The authors indicated that U-937, REH y Karpas-45 cell lines showed an MLT above 10kb and indicated that this may affect TERRA levels. However, it seems difficult to conclude about MLT and TERRA level, for example Raji and HAL-01 have a similar MTL of 6.8 and 7.3, respectively, and TERRAs were markedly different 2.0 and 0.4 respectively; THP1

and KOPN-8 have 4,6 and 5,4 MTL and 0.5 and 1.9 TERRA respectively suggesting that MTL and TERRAs seem to have a weak relationship.

4. In the section where TERRA levels were analyzed with respect of ploidy, it would be better to make the graphs with respect to the ploidy of the cells, it was very difficult to find the ploidy in the table and then analyzed the graph, at least indicate in the text which cells instead of given a number (i.e. x out of xx).
5. The major weakness of this study is the lack of data obtained from cells of ALL/AML patients carrying or not MLL-r.

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