Expression of p53 N-terminal isoforms in B-cell precursor acute lymphoblastic leukemia and its correlation with clinicopathological profiles:

In this paper authors used RT-PCR and western blot to investigate the expression of full length p53 isoforms such as TAp53, Delta40p53, Delta133p53 and p53beta in diagnostic marrow from BCP-ALL patients. They show that the expression of p53 isoforms is deregulated in BCP-ALL in the absence of TP53 mutation, with increased expression of alternative isoforms in relapse BCP-ALL. Using mathematical model on p53 isoforms mRNA expression they further predicted that: in primary BCP-ALL, p53 was predominantly in active oligomeric conformations dominated by TAp53, whereas p53 mostly existed in inactive quaternary conformations containing ≥ 2 Delta40 or Delta133p53 in relapse BCP-ALL.

The paper is interesting and supports the notion that "Overexpression or dysregulation of p53 isoforms can account for the development of cancers, as they can inhibit the canonical p53 functions" (Bourdon, J.-C et al 2005). However, there are some inconsistencies that should be clarified before publication can be recommended.

1) "semi-quantitative evaluation of the expression of two bona fide p53 target genes, MDM2 and CDKN1A revealed that both transcripts were markedly increased in primary BCP-ALL as compared to healthy donors, whereas only CDKN1A mRNA but not MDM2 was increased in relapse BCP-ALL (Figure 1b)".

p53 is a very well-known tumour suppressor protein which has a major role in regulation of cell cycle arrest and apoptotic pathways, in response to a plethora of stimuli. It serves as a transcription factor and directly and indirectly regulate several hundreds of different cellular genes including but not restricted to cell cycle (p21, 14-3-3), apoptosis (bax, puma, noxa), senescence (pai-1), autophagy (dram) etc (PMID: 30149602). In the present study authors just used 2 such targets CDKN1A and MDM2 to predict the p53 transactivation effect. Evaluating more target genes would give the readers more clear idea about the effects.

2) "Western blot analysis of bone marrow cells from patients confirmed that p53beta was one of the major p53 isoforms detected in BCP-ALL (Figure 4), whereas the p53 protein was barely detectable in cells from healthy donors".

a. Looking at the western blots, it seems Saos-2, BCP-ALL samples were run as two different western blots and then used for comparison. For comparison they should be run as a single gel/western blot.

b. Why was Saos-2 (cell line) used for comparison with BCP-ALL? since all the previous comparisons were done with healthy sibling donors, same control group should be included in the western blot also.
Also the western blot signal for p53 isoforms are very weak, so densitometry must be used to quantify isoform levels/normalization.

c. since this study is about primary and relapse BCL-ALL including all the subgroups in a single western blot would help the audience to understand more clearly.

3) regarding the mathematical model: authors should clarify if they considered the following effects while predicting the active and inactive configurations,

a. Δ40p53 can regulate distinct set of target genes other than just dominant negative effect on p53 (PMID: 23514281)

b. p53/p53 isoforms undergo posttranslational models which affect their stability/activity/function.

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.

No

Are the conclusions drawn adequately supported by the data shown?
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