Review of: "Deciphering TP53 mutant Cancer Evolution with Single-Cell Multi-Omics"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

In this manuscript, Rodriguez-Meira et al. examined the clonal evolution of TP53 mutation in secondary AML arising MPN and based on bulk genomic and TARGET-seq analyses they reported 4 major patterns of clonal evolution of TP53 mutations. They also integrated gene mutations and CNA and proposed clonal hierarchies in these diseases. Based on bioinformatic analyses, they reported erythroid skewing of TP53 mutated cells in secondary AML, which was subsequently validated by TP53 knockdown in MPN patient samples. They also develop a 51 genes TP53 mutated LSC signature that appeared to correlate with adverse outcome in patients. Finally, GSEA analysis revealed enrichment of inflammatory pathways in pre-LSC and whose activation was shown to enhance TP53 mutant clones both in vivo and in vitro.

In general, the manuscript was well written and relatively easy to understand. The issue is clinically relevant as there is an unmet clinical need to understand and improve the treatment outcome of TP53 mutated AML, many of which are secondary to antecedent MDS or MPN. Nonetheless, the manuscript in its present form suffered from a few drawbacks that precluded its publication. The authors may consider these comments in future submission.

1. There is a lack of connections between the aforementioned observations, for instance, clonal evolution and hierarchy, LSC gene signatures, erythroid skewing and inflammatory pathway activation and as such the manuscript appeared disjointed. The connectivity of various findings would have to be more clearly described.

2. While the observation about erythroid skewing and inflammatory signals are interesting, there is a lack of mechanistic evaluation. For the latter, more validation as to how TP53 mutant sAML gave rise to inflammatory signals should be performed.

3. The number of patient samples (N=2) for integrated analysis of mutation and CNA and for xenotransplantation was too small for any generalization to be made. In fact, the same two patients were used in these studies.

4. It was unclear how the chimera mouse model could be used to validate the observations about leukaemia survival on inflammation. The mouse cells used were Tp53 mutated haematopoietic cells but not leukaemia cells. A genuine leukaemia model should be used instead.