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

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TP53 is the most highly mutated gene in cancer and is strongly associated with poor clinical outcomes in multiple cancer subtypes. In most cases both TP53 alleles are affected often with one mutated and the other deleted and the cells lose most if not all of TP53s multiple functions including cell cycle arrest and apoptosis. Cancer is essentially a dynamic process of cellular , clonal evolution played out in the context of ecological pressures within the tissues involve and therapy .The remarkably high prevalence of mutational loss of TP53 function is then suggestive of convergent evolution and the prevalence of strong and common selective pressures for which loss of P53 function is an optimal fitness solution .

There is considerable insight into what those selective pressures are and they include cell intrinsic oncogenic stress, hypoxia and acidosis within tumour cores and, exposure to environmental or therapeutic genotoxins. I introduce these background details because in biology context is everything and the authors of the paper under review here are rather parsimonious in this respect which makes interpretation of their findings less robust.

In this paper the authors take advantage of paired samples from individual patients of pre malignant myeloproliferative neoplasms (MPN) and subsequent ‘secondary’ acute myeloid leukaemia (sAML) to trace the origins of the TP53 mutations that are clonally dominant , or selected in the AML phase in many but not all patients (20-35%). The authors employ a very elegant single cell method they have previously published called Target seek. This enables them to scrutinise transcriptional profiles in cells with defined genetic lesions- TP53 in this case and to compare them with cells that are at the same developmental stage but TP53 wild type. TP53 mutations present in the sAML are almost all double allele mutants or have one mutation coupled with deletion of the other allele .In the matched early stage MPN these same TP53 mutations are detectable but , unsurprisingly, at a significantly lower variant allele or cell frequency. The sAML with TP53 mutations were also highly aneuploid. This is described by the authors as a multi-hit clonal phenomenon. Pan genomic instability is a common feature of TP53 mutant clones in cancer but, also, effectively all clones in progressed cancer will be ‘multi-hit’ with sequential mutations and chromosomal changes. We don’t need a new term (with an implicit suggestion of novelty) for a well established , integral feature of cancer.

There are some unanticipated phenotypic features of the TP53 mutant progenitors but the claim to novelty here is with the suggestion that inflammatory signals may be the drivers for selection of these cells in their progression towards sAML . They provide support for his notion by a competitive transplant and haemopoeitic regeneration experiment (in immunodeficient mice) in which TP53 stem cells outcompete TP53 wildtype in the presence of an applied pro-inflammatory signal (poly I:C injection).

The conclusion is reasonable. The further interpretations and deductions less so. They suggest their findings herald a ‘conceptual advance’ in implicating both genetic and non genetic determinants of disease progression . This is questionable at several levels . Few cancer biologists would regard clonal evolution as an entirely cell intrinsic or purely genetic process reminiscent of Dawkin’s selfish gene concept for evolution in general. Recurrent genetic alterations , including TP53 ,are adaptive and emerge , or are selected , in the context of micro-environmental pressures. Inflammation is well recognised as a common component of cancer progression, especially in GI cancers.

This is an experimental paper not a review but nevertheless a more assiduous cross referencing to other TP53 research would be beneficial including the impact of TP53 on stem cell self renewal versus quiescence but particularly the paper by Wong et al published in Nature (2014, 518, 552). In this paper the authors characterise TP53 mutations in secondary AML and were able to trace these back to low level clones in the preceding clinical phase (mostly other cancers). Their plausible interpretation was that pre existing TP53 mutants were essentially neutral but in the context of genotoxic therapy were selected. These authors backed up their interpretation by demonstrating ,in a mouse model similar to that used by Rodriguez-Meira et al, that TP53 mutant clones had a competitive advantage in the face of genotoxic chemotherapy .It is unclear in the current study by Rodriguez-Meira et al what role, if any, chemotherapy in the MPN phase might have played in selecting the TP53 clones that were dominant in the subsequent sAML

Despite these caveats, this paper is technically excellent and throws further light on the likely role that micro-environmental inflammation plays in shaping clonal fitness in cancer . Finally there is unresolved conundrum in the current study with relevance to clinical management that deserves follow up . This is the question of why some (most?) patients with P53 mutant clones in the MPN stage do not progress to sAML? Is there a lower number of such cells? Is the TP53 mutation in the ‘wrong’ cell? Is there a difference in therapy for those that progress and those that do not?