

MDS and TP53: When One Hit Just Isn't Enough . . .

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In 1971, Alfred Knudson first proposed a “two-mutation hypothesis”—now commonly referred to as the “two-hit hypothesis”—for retinoblastoma, where a tumor suppressor gene gets inactivated in tumors derived from retinal cells. The idea was formulated based on the differential onset of disease in patients who inherited a pre-disposition compared to those that acquired the disease sporadically. The “first hit” turned out to be an inherited loss of function in one allele with the second allele getting mutated later in life. In non-inherited cases, both copies had to be lost in a single cell, making the likelihood of occurrence far lower and the disease substantially delayed in onset. Fast forward to 2020 and we can see catalogues of tumor suppressor genes that follow this pattern, from APC through to TP53 – all with this pattern that requires complete loss of the gene product to have its most damaging, disease accelerating, effects. Concomitant with this list of tumor suppressors is a huge wealth of genomic and clinical characterization that can now let the field determine the true impact of the different mutational states and a recent publication from Bernard et al., highlights the value of such datasets in the context of TP53 mutations.¹

TP53 is one of the most studied tumor suppressor genes in the cancer literature, being dubbed the “Guardian of the Genome”,² and strongly associated with sequence specific DNA-binding as well as DNA repair.³ As one of the most frequently mutated genes in human cancers, there are numerous types of mutations that have been described,⁴ ranging from heterozygous loss of function, dominant negative missense mutations and complete loss of function with patients commonly classed as in a binary fashion of “p53-mutant” or not. In hematological malignancies, numerous papers have associated p53 mutational status with poor prognosis,^{5–7} but relatively few papers have investigated much beyond the presence/absence of a mutation when it comes to biological and clinical implications in large datasets.

The Bernard manuscript does exactly this in a very large cohort of patients with myelodysplastic syndromes (MDS) by comparing TP53 allelic status. Comparing >3300 patients with complete clinical and genetic information, the paper divided MDS patients into those with a single hit (one allele of TP53 mutated) versus those with multiple hits (multiple alleles mutated). One third of patients were classed as monoallelic and the other two thirds as multi-hit, the latter of which suggests that the same cell might have lost both copies. The analysis showed that multi-hit TP53 patients were more likely to have complex karyotypes and a significantly higher risk of death and leukemic transformation.

Perhaps more interestingly, the paper also demonstrated that monoallelic TP53 mutations were virtually indistinguishable from non-mutant TP53 patients with respect to disease outcome and treatment response. This runs counter to data showing that single copy loss of TP53 leads to increased propensity to cancer development⁸ and increased accumulation of DNA-damage through reduced nucleotide excision repair,⁹ where one might expect poorer outcomes when a single copy is lost in humans. Also of interest is that a proportion of the TP53 multi-hit MDS patients might have bi-clonal mutations (ie, 2 different TP53 mutations in two different cells of origin) meaning that further resolution of the biological and clinical implications might be obtained through newly emerging single cell methods to profile patient samples.^{10,11}

Overall, this study is most interesting because it begins to engage with the complexity of single genes and their mutational status rather than binary outcomes of presence/absence. That said, there are further elements of heterogeneity involved (type of mutation, fitness of competing clones, microenvironmental changes, timing with other mutations, etc) that all might influence clinical outcomes. This will require large datasets with carefully curated clinical and genomic information (such as this paper does for MDS) and teams of people to undertake deeper analysis that reaches beyond the top 2 or 3 findings in the first manuscript. Hopefully, this paper stimulates such data mining within its consortium of MDS researchers but also acts to inspire collaborative groups in

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other hematological malignancies to build sufficiently large, well-characterized datasets with the power to reveal mutational heterogeneity and its potential clinical consequences.

References

1. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med.* 2020;26:1549–1556.
2. Lane DP. Cancer. p53, guardian of the genome. *Nature.* 1992;358:15–16.
3. Mantovani F, Collavin L, Del Sal G, et al. Mutant p53 as a guardian of the cancer cell. *Cell Death Different.* 2019;26:199–212.
4. Dutta S, Pregartner G, Rücker FG, et al. Functional classification of TP53 mutations in acute myeloid leukemia. *Cancers.* 2020;12:637.
5. Haase D, Stevenson KE, Neuberg D, et al. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. *Leukemia.* 2019;33:1747–1758.
6. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med.* 2011;364:2496–2506.
7. Kitagawa M, Yoshida S, Kuwata T, et al. p53 expression in myeloid cells of myelodysplastic syndromes. Association with evolution of overt leukemia. *Am J Pathol.* 1994;145:338–344.
8. van Boxtel R, Kuiper RV, Toonen PW, et al. Homozygous and heterozygous p53 knockout rats develop metastasizing sarcomas with high frequency. *Am J Pathol.* 2011;179:1616–1622.
9. Williams AB, Schumacher B. p53 in the DNA-damage-repair process. *Cold Spring Harb Perspect Med.* 2016;6:a026070.
10. Shepherd MS, Kent DG. Emerging single-cell tools are primed to reveal functional and molecular heterogeneity in malignant hematopoietic stem cells. *Curr Opin Hematol.* 2019;26:214–221.
11. Lee-Six H, Kent DG. Tracking hematopoietic stem cells and their progeny using whole-genome sequencing. *Exp Hematol.* 2020;83:12–24.