

Mitigating the Risk of t-MNs Development: *TP53* or Not *TP53*?

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Therapy-related myeloid neoplasms (t-MNs) are severe consequences of cytotoxic therapies used to treat solid tumors, nonmyeloid hematological cancers, or autoimmune disorders.¹ They consist of acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) and associate to poor prognostic features. The majority of t-MNs are believed to arise from pre-existing mutant hematopoietic stem cell (HSC) clones which do not undergo apoptosis in response to cytotoxic therapies and are thus favored under this selective pressure. Albeit numerous evidence demonstrated that the clonal hematopoiesis of indeterminate potential (CHIP) constitutes the soil for t-MNs development, it remains to be fully elucidated how individual therapies shape the selection and the evolution of specific mutant HSC clones. Understanding this aspect could enable modulating therapeutic regimens based on their effects on pre-existing mutant HSCs and thus reducing the risk of t-MNs development.

In a recent *Blood* article, Sperling and colleagues provided interesting clinical and experimental evidence to tackle this aspect.² The researchers first performed a mutational analysis of 416 patients diagnosed with t-MNs, including 40% of AML cases and 60% of MDS patients. This revealed the predominance of mutations in genes involved in DNA damage responses such as *TP53* and *PPM1D*, which were followed by common CHIP-associated mutations such as *TET2*, *DNMT3A*, *ASL1*, and *SRF2*. *PPM1D* and *TP53* mutations occurred more frequently in t-MNs compared to AML-MDS cases without prior exposure to chemoradiation therapies. *TP53* mutations, moreover, significantly associated to prior exposure to lenalidomide, hence suggesting that this drug could directly promote the development of t-MNs by selecting *TP53* mutant HSCs. To investigate this hypothesis, the authors performed competitive transplant assays using a murine model deficient for *Trp53* and sensitive to thalidomide analogs such as lenalidomide and pomalidomide. This revealed an outgrowth of *Trp53* knock-out HSCs over wild-type cells, which occurred only following exposure to lenalidomide but not to pomalidomide. To explain these findings on a mechanistic level, the authors built on their previous findings, reasoning that lenalidomide selective toxicity on wild-type HSCs could derive from its exclusive ability to degrade casein kinase alpha (CK1 α), a phenomenon that triggers p53-mediated apoptosis.³

Supporting this hypothesis, HSCs haploinsufficient for *Csnk1a* (the gene coding for CK1 α) were out-competed by wild-type cells in competitive transplant assays when exposed to lenalidomide. However, they did not show a competitive disadvantage upon treatment with pomalidomide or iberdomide, 2 thalidomide analogs which do not degrade CK1 α . These data suggest an interesting model linking lenalidomide and t-MNs bearing *TP53* mutations. In this model (Figure 1), CK1 α degradation, selectively induced by lenalidomide but not by other thalidomide analogs, induces p53-mediated apoptosis in wild-type cells but not in *TP53* mutant HSCs, hence positively selecting them. Although the researchers provided some experimental evidence excluding the possibility that lenalidomide could select for HSCs bearing other CHIP-associated mutations (ie, *Dnmt3A*, *Tet2*, *Asxl*, *Pmp1d*, *Ezh2*), it remains to be investigated whether this holds true for other thalidomide analogs. Further investigating these aspects will be important to define whether the careful choice of thalidomide analogs in chemotherapy regimens may allow to mitigate the risk of developing t-MNs.

As the patients analyzed in Sperling's study included multiple myeloma cases, the vast majority of which were exposed to both lenalidomide and proteasome inhibitors, one may argue that the expansion of *TP53* mutant HSC clones may result from the combined exposure of both drugs. The clinical and experimental evidence provided by the authors, however, do not support this possibility. On one side, the multivariate analysis the authors performed to adjust for the confounding effects of multiple exposure confirmed the significant association of *TP53* mutation and lenalidomide exposure. On the other side, in vitro long-term competitive experiments using an immortalized murine hematopoietic stem/progenitors line showed that proteasome

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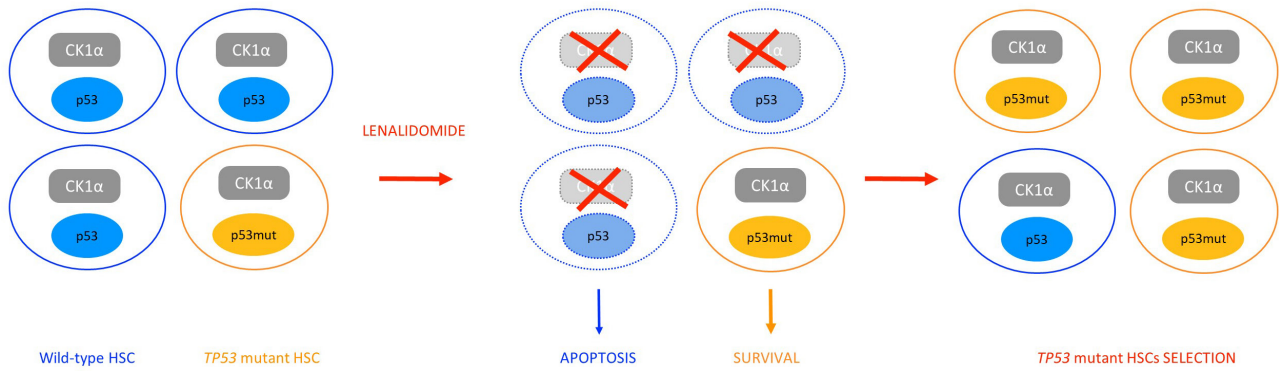


Figure 1. By degrading CK1α, lenalidomide induces p53-dependent apoptosis in wild-type hematopoietic stem cells but not in TP53 mutant clones, hence favoring their positive selection and, ultimately, the development of t-MNs. CK1α = casein kinase alpha; t-MNs = therapy-related myeloid neoplasms.

inhibitors such as bortezomib or carfilzomib conferred only a mild proliferative advantage to *Trp53* mutant cells in contrast to the pronounced proliferative advantage provided by lenalidomide exposure.

To conclude, the study by Sperling and colleagues provided an interesting molecular and functional characterization of the interplay linking patients genotype and specific cytotoxic drugs in driving the selection of premalignant clones. This has important consequences as it suggest at least 2 strategies to possibly reduce the risk of developing t-MNs, namely screening patients undergoing lenalidomide-based therapies for *TP53* mutant CHIP and/or adapting chemotherapy regimens by choosing the appropriate thalidomide analog.

DISCLOSURES

The author has no conflicts of interest to disclose.

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