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Patterns of mutations in *TP53* mutated AML

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Abstract

TP53 mutated acute myeloid leukemia (AML) responds poorly to chemotherapy and has a short overall survival rate with a median of 5–9 months. Poor outcomes in *TP53* mutated AML following chemotherapy have been observed and treatment options remain limited, although the presence of *TP53* mutations alone should not be a barrier to therapy. Decitabine is emerging as an alternative treatment option for patients with *TP53* mutated AML, although the agent has not been associated with deep molecular remissions and requires additional consolidation. The clinical and genomic characteristics of *TP53* mutated AML are reviewed in this paper.

Keywords

Acute myeloid leukemia; AML; clonal hematopoiesis of indeterminate potential; CHIP; decitabine; myelodysplastic syndromes; MDS; mutation patterns; *TP53*

Introduction

TP53 mutated acute myeloid leukemia (AML) forms a subset of AML with poor response to chemotherapy (28% - 42% overall response rates) [1–3] and overall survival short (median survivals of 5–9 months)[1, 2, 4–7]. In this brief manuscript we will review the clinical and genomic characteristics of *TP53* mutated AML.

TP53 mutations in AML are associated with older age, lower blast counts (both in the bone marrow and in the peripheral blood), adverse risk karyotypes, and exposure to antecedent chemotherapy [2, 8–10]. They are independently prognostic in multiple studies when accounting for age and cytogenetics [2, 3, 5, 6]. In general, *TP53* mutations may occur across nearly all FAB morphologic subtypes, although there is a modest enrichment in M6-erythroleukemias (25% -36%) [2, 11]. Given this diversity of morphologies associated with *TP53* mutations, expression signatures associated with *TP53* mutations are confounded by

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Conflict of Interest

The author declares no conflicts of interest.

the broader signatures associated with morphology, and a specific expression signature associated with *TP53* mutations has not yet been identified [12].

Although *TP53* mutations are among the most prevalent somatic variants associated with all cancer types, the incidence of *TP53* mutations in AML is lower than patterns observed in solid tumors. For example, among patients with ovarian, colorectal, esophageal, and head & neck tumors, the incidence of *TP53* mutations is 48%, 43%, 43%, and 41%, respectively. Whereas the incidence of *TP53* mutations in AML is 12.7% [13]. Likewise, Li-Fraumeni syndrome is associated with germline *TP53* mutations, but AML is unusual among Li-Fraumeni patients and only constitutes ~5% of Li-Fraumeni associated malignancies [14]. These findings suggest that cooperating events are required for leukemic progression, and perhaps that these occur less commonly in hematopoietic cells compared with other tissue types.

Mutation patterns

Mutations that co-occur with *TP53* form unique signatures. *TP53* mutations frequently co-occur with karyotypic structural alterations, especially large deletions and other abnormalities involving chromosomes 5, 7, 17, and with events involving chromothripsis [3, 5, 6, 12, 15–23]. In contrast, the single nucleotide variants in recurrent AML genes (eg, *DNMT3A*, *NPM1*, *FLT3*, *IDH1*, *IDH2*, *TET2*, etc) are observed with reduced frequency in *TP53* mutated AML, suggesting a bias in cooperative functionality, although one cannot exclude differences in the predilection for mutation acquisition. The distinct patterns of adverse outcomes and mutational co-occurrence have lead multiple groups to cluster *TP53* mutated into a unique subgroup of AML [5, 12].

Poor outcomes in *TP53* mutated AML following chemotherapy have been observed across a wide range of studies [1, 2, 4–7]. Activation of TP53 is a critical mechanism for response to a cytotoxic chemotherapy [24, 25]. Therefore, it is not surprising that *TP53* mutations are enriched in treatment-related myeloid neoplasms and that *TP53*-mutated AML responds poorly to chemotherapy that induces DNA damage and cellular stress and cell death via TP53-activating mechanisms.

Cell-intrinsic chemotherapy resistance provided by *TP53* mutations has also been observed in clonal disorders that antecede AML. In patients with clonal hematopoiesis of indeterminate potential (CHIP), *TP53* mutations or deletions in 17p have been observed [26–28]. In these studies, only mutations in *DNMT3A*, *TET2*, and *ASXL1* are more commonly observed than *TP53* mutations.

Pre-existing clones with *TP53* mutations have been implicated in the pathogenesis of treatment-related myeloid neoplasms. Analysis of patients with treatment-related AML and myelodysplastic syndromes (MDS) associated with *TP53* mutations found that the associated *TP53* variants could be observed in a small fraction of cells prior to the patient's initial exposure to chemotherapy [29]. Thus, the *TP53* mutations appear to provide a selective advantage in the associated hematopoietic stem/progenitor clones, which facilitates subsequent outgrowth and expansion during this evolutionary bottleneck. Subsequent studies

have evaluated a broader series of patients with CHIP and compared subjects who had been previously exposed to chemotherapy or had not had prior chemotherapy treatment [30, 31]. In these studies, variants in *TP53* and in *PPM1D* were strongly enriched in the patients with prior chemotherapy exposure. Thus, *TP53* mutations appear to provide an intrinsic selective advantage during chemotherapy-induced evolutionary pressure and the application of additional chemotherapy is logically unlikely to provide an easy solution.

The presence of *TP53* mutations in “pre-leukemic” states such as CHIP suggests that these variants occur early during clonal evolution. In AML, *TP53* variant allele frequencies are typically high and are nearly universally stable at relapse, again suggesting that these are early events during clonal evolution and associated with the founding clone [2, 6, 32]. One exception should be noted. *TP53* mutations have been associated with AML progressing from polycythemia vera and essential thrombocythemia suggesting that they may facilitate leukemic progression of established clonal disorders under some circumstances [33].

Genomic instability

Genomic instability has been attributed to *TP53* dysfunction. We reviewed the mutation patterns observed during exome sequencing in 23 patients with mutated *TP53* and compared these with 213 patients with wild-type *TP53* [32, 34]. Interestingly, we did not observe an increase in the number of age-adjusted single nucleotide variants in *TP53* mutated cases, and both groups exhibited evidence of age-associated mutagenesis, with increased numbers of mutations in older vs younger patients (Figure 1A). Likewise, the mutation spectrum of exome-associated mutations was unchanged between *TP53*-mutated and *TP53*-wild-type cases (Figure 1B). These data suggest that *TP53* mutations do not induce global genomic instability. Rather, only specific types of mutations are noted with greater frequency in *TP53*-mutated AML. As noted above, *TP53*-mutations co-occur with increased numbers of large cytogenetic events, chromothripsis, and marker chromosomes [18, 35]. However, they are not associated with an increase in single nucleotide variants, suggesting specificity and cooperative pathogenicity associated with these co-occurring genomic variants, rather than non-specific genomic noise.

Mutations may co-exist within founding clones, subclones, or may exist in alternative clones which are unrelated to the malignant clone. To understand the order of mutagenesis in *TP53* mutated AML, we evaluated the relative variant allele frequencies of co-occurring mutations within published datasets [5, 6, 32, 34]. Two patterns emerged. First, mutations in *TP53* and epigenetic genes (*DNMT3A*, *TET2*, *IDH1*, *IDH2*) and transcription factors (*NPM1*, *CEBPA*, *RUNX1*) typically co-localized to the founding clone, and occasionally, the *TP53* VAF was lower than the co-occurring mutation, suggesting that the *TP53* mutation either existed in an alternative clone, or was contributing to subclonal evolution of a previously established clone (Figure 1C). In contrast, mutations in activated signaling pathways (*FLT3*, *RAS*, *PTPN11*, *BCOR*, *JAK2*, *NFI*) and in polycomb pathways (*SF3B1*, *KDM6A*, *SRSF2*) occurred typically in subclones, suggesting that these variants can productively accelerate *TP53* AML during clonal evolution (Figure 1D). Mutations in *ASXL1*, *CBL*, and *U2AF1* occurred almost equally in subclones of *TP53*, and with *TP53* as a variant in an emerging subclone. These data demonstrate that *TP53* mutations typically occur within the founding

clone, that common progression mutations can also productively interact with *TP53* during clonal evolution, and that occasionally *TP53* mutations may act as progression events within established clonal architecture.

Although *TP53* has been described as a tumor suppressor, nearly 75% of variants are missense, rather than non-sense or splice-site variants that might be more obviously associated with loss-of-function consequences. Likewise, patterns of variant location within the gene present a mixed message: although missense variants occur across all domains of the gene, recurrent hot-spot variants are also observed in AML and in solid tumors (eg, R175H, R248Q, R273H, and Y220C) [36]. The majority of mutations occur within the DNA binding domain of TP53, and these typically result in reduced or absent DNA binding [36]. However, these variants do not always result in simple loss-of-function, and frequently can induce dominant-negative effects on the residual wild-type protein [37]. In cell-based studies, over-expression of missense variants on a background of *TP53* deficiency has been associated with gain-of-function phenotypes, especially involving pathogenic features including augmented tumor cell proliferation, invasion, migration, chemotherapy resistance, and metastasis [38–40]. Likewise, overexpression of wild-type *TP53* in the context of tumor cells with null vs mutant *TP53* tumor cells lead to the incomplete restoration of the mutant expression signatures, again, suggesting novel functions of the mutant proteins that could not be restored by re-expression of the wild-type allele [41]. The expression consequence of different variants varied, depending on the mutation; R172H had the greatest effect (and this is one of the most common missense variants), whereas expression of wild-type TP53 could abrogate the effects of R270H to a greater degree (a DNA contact mutation) [41]. Similar studies have been performed using transgenic strategies. In vivo, the expression of missense variants has been associated with more aggressive tumors, more rapid proliferation, and augmented metastasis [42, 43]. Together, these data suggest that missense mutations may frequently lead to pathogenic gain-of-function effects, which may facilitate outgrowth of more aggressive and invasive tumor cells.

Wild-type TP53 protein has a short half-life and cannot typically be observed by simple immunohistochemistry. Many of the missense mutations lead to protein stabilization that is adequate to visualize with immunohistochemistry [44–47]. This approach provides a fairly sensitive and specific methodology for rapidly identifying *TP53* mutated patients who could be enrolled on clinical trials. Naturally, patients with nonsense mutations or bi-allelic deletions may not be identified, and these “false negatives” would need to be accounted for. Mechanisms of high mutant TP53 expression have not been clearly elucidated in AML, but may include decreased ubiquitination [48] and disruption of normal MDM2 negative feedback mechanisms on *TP53* expression [47, 49]. Overexpression likely contributes to or augments dominant-negative effects and gain-of-function phenotypes imposed by the associated missense variants.

The mechanisms of leukemogenesis in *TP53* mutated AML remain unclear. Within the subset of erythroleukemia, direct cross-talk between Gata1 and Tp53 has been described, suggesting potential lineage-restricted leukemic activity [50]. The frequent co-occurrence of chromosomal abnormalities in chromosomes 5 and 7 suggests that specific additional pathways must be modified to transition from CHIP to AML.

Treatment options

Treatment options remain limited for *TP53* mutated AML. It is clear that cytotoxic chemotherapy has limited activity, likely due to cell-intrinsic resistance to TP53-induced apoptosis in cells that lack TP53 or have dysregulated TP53 function. However, despite these discouraging results, *TP53*-mutated AML patients who did not receive chemotherapy fared even worse [1], so the presence of *TP53* mutations alone should not be an absolute barrier to therapy. Decitabine, when used at low doses does not lead to direct cytotoxicity. Instead, as a cytosine moiety that cannot be methylated, its incorporation into DNA leads to alterations in epigenetic signatures [32, 51]. Multiple groups have noted that the presence of adverse risk karyotypes did not impact the response rates or overall survival of patients treated with decitabine [52–56]. Several studies evaluating response to decitabine based on mutation profile have observed consistent responses in AML and MDS patients with *TP53* variants [19, 32, 57]. However, despite initial responses to decitabine, mutation clearance appears to be incomplete, and relapses are commonplace [32]. Therefore, additional combinations will need to be explored to determine whether consolidation with alternative therapies or with stem cell transplantation may overcome molecular residual disease and relapse risk following decitabine responses.

Because TP53 mutated protein consistently leads to protein stabilization and overexpression, there has been an interest to develop therapeutic strategies that are capable of destabilizing accumulated mutant TP53 protein [36, 47, 49]. It is unclear at this time whether these will necessarily be mutation specific, or whether drugs can be developed that will destabilize diverse mutant forms. In addition, there has been interest in identifying pathways that become necessary for cell survival in the presence of *TP53* mutations, as these could function as synthetic lethality strategies [58]. This may offer an alternative approach, although it will be important to determine whether these strategies result in cell-type specificity or if they might become effective across diverse cancer cell types.

Conclusion

In summary, *TP53* mutated AML poses a significant problem. These cases have frequently emerged following chemotherapy exposure, and TP53 dysfunction facilitates chemoresistance. Although complex karyotypes have been a hallmark of *TP53*-mutated AML, these tumors do not accumulate an excess of single nucleotide variants, suggesting either that alterations led to increased propensity to tolerate only certain classes of mutagenesis or that alterations in specific pathways are required for leukemic progression. Decitabine is emerging as an alternative treatment option for patients with *TP53* mutated AML, although this has not been associated with deep molecular remissions and without additional consolidation, relapses remain commonplace. Future studies will be needed to elucidate these progression events and to identify alternative treatment strategies.

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Figure 1.

A. The number of Tier 1 (exome) mutations observed in AML patients evaluated at Washington University using exome sequencing [32, 34]. Cases highlighted in red had associated *TP53* mutations. Cases in black had *TP53* wild-type. **B.** Mutation spectrum from patients described in A. **C** and **D.** Mutation co-occurrence patterns in AML patients with *TP53* mutations from published series [5, 6, 32, 34]. These segregated into two groups: cases with *TP53* mutations and mutations in mutations in *TP53* and epigenetic genes (*DNMT3A*, *TET2*, *IDH1*, *IDH2*) and transcription factors (*NPM1*, *CEBPA*, *RUNX1*) typically co-localized to the founding clone (**C**), whereas mutations in activated signaling pathways (*FLT3*, *RAS*, *PTPN11*, *BCOR*, *JAK2*, *NF1*) and in polycomb pathways (*SF3B1*, *KDM6A*, *SRSF2*) occurred typically in subclones of the *TP53* mutant clone (**D**).