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TP53 and therapy-related myeloid neoplasms

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ABSTRACT

Therapy-related myeloid neoplasms (*t*-MNs) are the most serious late complications in patients treated with traditional cytotoxic chemotherapy and/or radiation. T-MNs are aggressive and chemorefractory hematologic malignancies, with a median survival of less than 6 months. *TP53* mutations are highly enriched in t-MN patients, though the mechanism for this selective enrichment has only come to light over the past several years. In this review, we discuss the history and function of p53, and the role of *TP53* mutations in the origin and progression of *t*-MNs. Emerging data has begun to elucidate who may be at highest risk of developing *t*-MNs, which ideally will enable us to develop preventative strategies for this devastating disease. As *t*-MNs may not be avoidable, novel therapies are urgently needed for this patient group and are underway as exemplified by recent investigation in restoring wild-type p53 function as well as directly targeting *TP53* mutant variants. With better prevention and treatment, outcomes will hopefully begin to improve in the near future.

1. Introduction

Therapy-related myeloid neoplasms (*t*-MNs); including myelodysplastic syndromes (*t*-MDS), acute myeloid leukemia (*t*-AML) and MDS/myeloproliferative neoplasms (*t*-MDS/MPN) are clonal hematopoietic disorders that usually develop 1–5 years following treatment with cytotoxic chemotherapy and/or radiotherapy [1]. They have a uniformly poor prognosis regardless of morphology and as such, are collectively categorized as *t*-MNs by the World Health Organization (WHO) [2]. The classic presentation of *t*-MNs occurs after exposure to alkylating agents, with associated loss of all or part chromosome 5 and/or 7, and commonly clinically presents as *t*-MDS after an average latency period of five years. On the other hand, *t*-MNs that develop after receiving topoisomerase II inhibitors are characterized by balanced rearrangements enriched for those involving the *MLL* gene, have a shorter latency period of 1–2 years and present overtly as *t*-AML [3]. Currently, it is estimated that *t*-MNs constitute 10–20% of all AML/MDS.

Several features distinguish *t*-MNs from *de novo* disease. First, *t*-MNs have a higher frequency of complex cytogenetics, *TP53* mutations and a poor response to conventional chemotherapy [4,5]. *TP53*, located on chromosome 17p13, encodes the p53 tumor suppressor protein. This integral transcription factor responds to DNA damage by activating transcriptional programs for DNA repair and activating apoptosis if necessary [6]. *TP53* mutations are observed in more than 50% of solid tumors but occur in only ~5–10% of *de novo* MDS/AML [7,8]. In comparison, *TP53* is the most commonly mutated gene in *t*-MNs, occurring in ~30% of cases [9]. It was previously thought that this selective enrichment was secondary to the direct mutagenic effects of chemotherapy. However, more recently, it has been shown that hematopoietic stem/progenitor cells (HSPCs) harboring *TP53* mutations can be present prior to the development of t-MN, suggesting that these chemotherapy-resistant clones preferentially expand after treatment [10]. This review

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will further examine mutations in *TP53*, its role in the evolution of *t*-MNs, and subsequent therapeutic implications.

2. Mechanisms of *TP53* tumorigenesis

TP53, located on chromosome 17p13.1, is comprised of 11 exons that encode a 393 amino acid nuclear phosphoprotein [11]. This extensively studied cellular protein has risen to unprecedented prominence since its discovery in 1979. During an era focused on cancer-causing viruses, p53 was first identified when it immunoprecipitated as part of a complex with SV40 large T-antigen, a protein derived from the SV40 virus [12]. The observation that SV40 was associated with overexpression of p53 in transformed cells lead to the conclusion that p53 was an oncogene, although It took another decade to realize that the p53 clones capable of transformation were actually mutated [12]. This was firmly established when the previously tested clones were compared to sequenced wild type p53 derived from normal murine tissue [12]. After many subsequent studies, p53 was further characterized as a transcription factor, with an *N*-terminal transactivation domain, a core DNA-binding domain (DBD), and a *C*-terminal regulatory domain. When p53 is activated in response to cellular stress, it regulates a multitude of genes to induce apoptosis, DNA repair, cell differentiation, and growth arrest.

Given its vital role in cellular integrity, p53 is also highly regulated. Murine double minute-2 (MDM2) and murine double minute-4 (MDM4), also known as murine double minute-X (MDMX), discovered in 1992 and 1994 respectively, are homologous proteins that inhibit p53 activity by binding to the *N*-terminal transactivation domain [13,14]. MDM2 also acts as an E3-ubiquitin ligase that targets p53 for degradation by the 26*S* proteasome [15]. In turn, the *MDM2* gene is targeted by p53, forming an elegant negative feedback loop that keeps p53 activity low until exposed to genomic stress [16]. Such observations led to the reverent naming of p53 as “guardian of the genome” in 1992 [17].

Unsurprisingly, p53 dysfunction is mechanistically implicated in a broad group of malignancies. Hematologic malignancies notably have fewer *TP53* mutations compared to solid tumors. However, this decreased incidence does not diminish its significance. Multiple studies have shown that *TP53* alterations are associated with complex and monosomal karyotypes, and invariably a poor prognosis [4,18–21]. Further studies have shown that the *TP53* mutational burden, also known as variant allele frequency (VAF), is directly proportional to the number of cytogenetic abnormalities and is an independent predictor of inferior overall survival (OS) in patients with secondary AML and myelodysplastic syndrome [22,23].

The majority of *TP53* mutations are somatic missense mutations located in the DNA-binding domain that form a stable protein but impairs its sequence-specific DNA-binding activity [24]. Furthermore, it is not uncommon for *TP53* mutations to be followed by the cytogenetic loss of the wild-type allele by either loss of heterozygosity or uniparental disomy events [4]. In the instances that the second allele remains uncompromised and produces a wild-type protein, its function can still be inhibited by the dominant-negative effect of the mutant p53 [25]. Moreover, emerging evidence has established that variant specific *TP53* mutational consequences exist. For example, mutant p53 does not only cause loss of function through the aforementioned mechanisms but also gains new tumorigenic properties of its own. This gain-of-function (GOF) hypothesis has garnered traction after it was demonstrated that transfection of mutant p53 in cell lines lacking p53 caused enhanced tumorigenesis in mice [25,26]. Currently, it is believed that such GOF properties are largely indirect and related to mutant p53's ability to bind to other cellular proteins which alters their activity, the most pivotal of which are p63 and p73 [27]. These transcription factors are members of the p53 family and have roles in suppressing tumorigenesis. This was shown when knock-in mice with mutant p53 caused functional inactivation of p63 and p73, leading to increase transformation capacity, DNA synthesis and metastatic potential [27].

3. *TP53* mutations in t-MN

TP53 is the most commonly mutated gene in *t*-MNs, occurring in ~20–40% of cases, compared to ~5–10% in *de novo* MDS/AML [5]. Historically, it was thought that the increased frequency of *TP53* mutations in *t*-MNs was related to the direct cytotoxic effect of chemotherapy and radiation on hematopoietic stem and progenitor cell (HSPC) DNA. However, increasing evidence over the past few years suggests that pre-leukemic clones harboring a somatic *TP53* mutation preferentially expanded after cytotoxic treatment [1]. Wong et al. sequenced the genome of 22 cases of *t*-AML and compared it to 49 cases of *de novo* AML, demonstrating that the number of single nucleotide variants (SNVs) and small insertions or deletions (indels) were similar [10]. Moreover, the percentage of transversions were also comparable, disputing the previous hypothesis that chemotherapy induces cytotoxic damage and an increased mutational burden. This was further corroborated in a separate study by OK et al. when they sequenced *TP53* mutations in *t*-MNs and *de novo* MDS/AML and found that their mutation patterns and allelic frequencies were strikingly similar [5]. Though the overall mutational burden was similar, there were distinctive subsets of mutated genes present in t-MN and *de novo* AML/MDS. In concordance with prior studies, *TP53* mutations were significantly higher in t-MN but had fewer driver mutations such as *NPM1* and *DNMT3A*. Interestingly, it has also been shown that *TP53* mutations are mutually exclusive with other genes such as *FLT3, MDM2,* and *ARF* [8].

To further elucidate the cause of this selective enrichment, Wong and colleagues identified four cases of t-MN in which the specific *TP53* mutation was present 3–6 years prior to the development of t-MN at low frequencies (0.003–0.7%). This clonal advantage was directly demonstrated when murine *TP53*+/-HSPCs were treated with *N*-ethyl-*N*-nitrosurea. Collectively, this supports the model that acquired age-related *TP53* mutant HSPCs are resistant to chemotherapy and contribute to the complex cytogenetics associated with *t*-MNs. However, in the other three cases, *TP53* mutations were not identified in the pre-treatment sample, which suggests that chemotherapy and/or radiation may induce these mutations in a subset of patients or that the variant was below the threshold level of detection utilized in the above assays.

Similarly, on a broader level, it has been shown that individuals with somatic mutations with a mutant allele frequency higher than 2%, defined as clonal hematopoiesis of indeterminant potential (CHIP), have an increased risk of developing t-MN. CHIP can be seen in 1% of healthy individuals, with an increased frequency of up to 10% in those over age 70 [28,29]. The genes mutated in CHIP, such as *ASXL1*, *TET2*, *TP53*, and *DNMT3A*, are frequently mutated in myeloid malignancies. While CHIP in the general population is largely age-related and increases slowly over time [30–32], treatment with cytotoxic chemotherapy or radiation in cancer patients precipitates rapid expansion of their underlying CHIP clones leading to *t*-MNs [33]. This is in line with previous studies that suggest cytotoxic therapy creates an environment that selects for pre-existing, mutated clones [33], and several studies have identified CHIP in 62–71% of t-MN patients at the time of primary malignancy [34–36]. However, there is not yet a consensus on which CHIP mutations are the most clinically relevant. There is also no evidence that CHIP is the sole driver in the development of *t*-MNs. Inherited single nucleotide polymorphisms in critical regulation pathways may also be potential predisposing factors. Ellis et al. observed that although individual *MDM2* SNP309 and *TP53* codon 72 polymorphisms did not increase risk of t-MN, there was an interactive effect in those carrying both variants [37]. Additionally, in a very large sequencing study of the Women's Health Initiative, 100% of patients with *TP53* (n = 21) and *IDH* 1/2 (n = 15) mutations ultimately developed disease, providing a strong argument that certain variants have a much higher phenotypic penetrance [38]. Together, these data would suggest that avoidance of adjuvant therapies may be indicated in patients with specific mutant clones at baseline, although future studies are required in order to best quantitate the exact benefits/risks of this decision.

4. Prognosis

Multiple studies have shown that *TP53* mutations are associated with complex karyotype and poor prognosis [18,20,21,39,40]. Grossmann and colleagues demonstrated using both univariable and multivariable Cox regression analyses that patients with *TP53* mutations had median overall survival (OS) of just 4.6 months as compared to 35.6 months in non-mutated cases. Even in the complex karyotype cohort, those with *TP53* mutations had an inferior outcome, with 3-year OS 0% vs. 27.9%. Similarly, Bowen and colleagues showed that in a multivariate analysis adjusting for various factors, including *de novo*/secondary AML and cytogenetic risk group, *TP53* mutations were independently associated with reduced OS. Of the patients with adverse cytogenetics, *TP53* mutations were associated with significant reduction in complete response (CR) rates, disease-free survival (DFS) and OS. Moreover, for the few patients that achieve CR and were able to undergo a hematopoietic stem cell transplant, ~70% relapsed within 6 months and 3-year OS was only 15% [41,42]. In patients with *t*-MNs and *TP53* mutations, the median OS was 6.1 months. This was comparable in both patients with *TP53* t-MN and *de novo* MDS/AML. *TP53* mutation was again shown to be an independent risk factor in this cohort, using univariate and multivariate analyses [5].

5. Therapeutic implications

Novel mechanistic and translational studies concerning both p53 and *t*-MNs have opened up innovative prevention and treatment strategies, though much remains to be ascertained. The theory that chemotherapy confers a competitive advantage to HSPCs with specific, age-related “fitness” mutations, such as *TP53*, continues to gain traction. However, there has been no prospective study to validate CHIP as a predictive biomarker for t-MN risk stratification. Additionally, the burden of germline single nucleotide polymorphisms in the development of *t*-MNs has yet to be fully characterized. Such information could help mitigate the occurrence of disease by avoiding conventional chemotherapy in those identified as high risk. Given the poor response rates and dismal outcomes in *t*-MNs, all efforts to prevent *t*-MNs are of the utmost importance. Currently, patients treated with standard anthracycline and cytarabine based induction therapy have response rates of only 20–30% and median survivals of 4–6 months [18,21]. Due to this, and the older age of this cohort, hypomethylating agents (HMA) have emerged as preferred treatment with CR rate of 20–30% and median OS of 6–12 months, which although very poor is superior to historical intensive chemotherapy outcomes [43–45].

Pharmacologic strategies to both stabilize wild type and mutant p53 resulting in restoration of its tumor-suppressive function are in development for myeloid malignancies. The most promising thus far is APR-246 which is a prodrug that is converted to methylene quinuclidinone (MQ) and binds covalently to the mutant p53 core domain, restoring the upregulation of apoptotic transcriptional programs (Fig. 1) [46,47]. More recently in a phase Ib/II study, APR-246 was combined with azacitidine to treat patients with *TP53* mutant MDS and AML, of which 5/12 patients had t-MN. Notably in evaluable patients (n = 11), the combination of APR-246 and azacitidine had an overall response rate of 100%, with 82% of patients achieving CR. Additionally, responses were accompanied by deep molecular remissions with a median VAF of 0.3% in NGS negative patients [48].

On the other hand, targeted therapy to reverse wild type p53 inactivation are also in development. The majority of these therapies aim to disrupt wild type p53 and MDM2/MDMX interactions (Fig. 2). Several MDM2 inhibitors have advanced to clinical studies and are being studied as monotherapy as well as in combination with cytarabine, venetoclax, trametinib or hypomethylating agents [49]. A chief concern of MDM2 inhibitor therapy is the effect of p53 activation in normal cells. It has also been shown that p53 mutations are selected for or acquired while on MDM2 inhibitor therapy, though the significance of this is not yet clear [50]. Another potential mechanism of resistance is increased levels of MDM4. To address this, dual MDM2/MDMX inhibitors are under evaluation; specifically ALRN-6924 is being studied in a phase 1 clinical trial. Preliminary results presented at the 2018 ASH annual meeting reported no objective responses with single agent ALRN-6924 but did show clinical activity in combination with low-dose Ara-C in MDS patients [51].

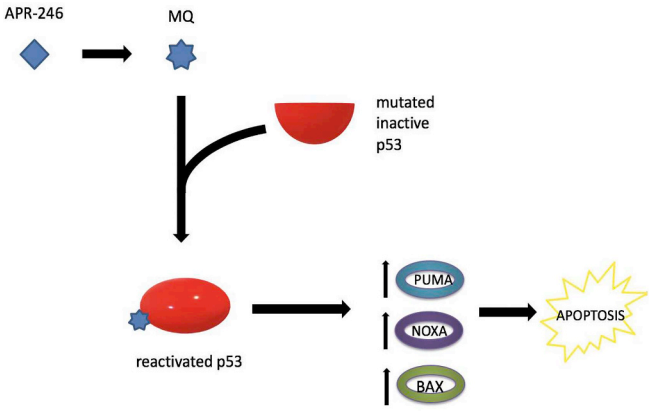

Fig. 1. APR-246 is converted to methylene quinuclidinone (MQ) and binds covalently to the mutant p53 core domain, restoring the upregulation of apoptotic transcriptional programs.

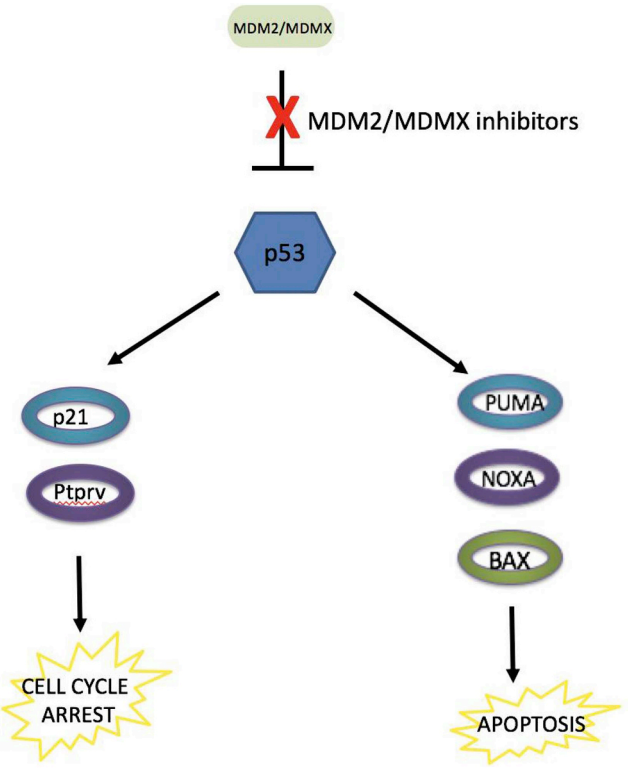

Fig. 2. MDM2/MDMX inhibitors aim to reverse wild type p53 inactivation.

6. Summary

In summary, *t*-MNs harbor a high frequency of *TP53* mutations, which in turn are associated with complex karyotype and poor survival. This selective enrichment is due to the preferential expansion of somatic *TP53* mutated HPSCs which can be present years prior to the diagnosis of t-MN. Consequently, p53 dysfunction leads to genetic instability and suboptimal response to chemotherapy. Despite the new discoveries in the pathobiology of *t*-MNs, many questions remain, and therapeutic progress is still lacking. Though there are novel p53-based therapies currently in development, it is also of critical importance to determine which patients are high risk in order to prevent disease occurrence altogether.

Practice Points

- Therapy-related myeloid neoplasms are frequently associated w/*TP53* mutations, complex karyotypes and poor prognosis
- They respond poorly to conventional chemotherapy and have high relapse rates after hematopoietic stem cell transplant
- Hypomethylating agents are the preferred treatment for this disease, though there remains a significant need for improvement

Research Agenda

- There are several p53-directed therapies currently in development, such as APR-246 and ALRN-6924
- Identifying risk factors to prevent therapy-related myeloid neoplasms altogether is of equal, or perhaps greater importance

Conflicts of interest

Dr. Chung and Dr. Padron have no conflicts of interest to report. Dr. Sallman receives research funding from Celgene.

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