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Implications of *TP53* Gene Mutations in Myelodysplastic Syndromes: A Review

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Abstract

TP53 is a tumor suppressor gene that has come to be known as the Guardian of the Genome. Mutations in this tumor suppressor are found in at least half of all cancers. P53 plays a role in arresting the cell cycle and inducing apoptosis; it can be activated through a variety of means such as genotoxic stress, dysfunctional telomeres, oncogenic signaling, abnormal microtubules, ribosome biogenesis, and a variety of other modes. *TP53* mutations are less frequently found in myelodysplastic syndromes; however, knowledge of *TP53* mutations can more accurately predict a patient's outcome. In general, mutations in *TP53* correlate to a poor outcome and higher incidence of transformation to acute myeloid leukemia in patients with isolated del5q or a complex karyotype.

Keywords: Myelodysplastic syndromes; *TP53*; Acute myeloid leukemia; 5q- Syndrome; Tumor suppressors; Genetic mutations

Abbreviations

TP53: Tumor Protein 53; MDS: Myelodysplastic Syndromes; AML: Acute Myeloid Leukemia; MDM2: Mouse Double Minute 2; ATM: Ataxia Telangiectasia-mutated; ATR: ATM-Rad3-related; PI3K: Phosphoinositide 3-kinase; MRN: MRE11-Rad50-Nbs1; CHK: Check Point Kinase 2; CDK: Cyclin-dependent Kinase; MPF: Maturation-promoting Factor; CDC2: Cell Division Cell 2; CDC25C: Cell Division Cell 25 C; Rb: Retinoblastoma Protein; TRF2: Telomere Repeat-binding Factor 2; ARF: Alternate Reading Frame; $P14^{ARF}$: Alternate Reading Frame Protein 14; Myc: Avian Myelocytomatosis Viral Oncogene Homolog; Ras: Rat Sarcoma Viral Oncogene Homolog; RPL11: Ribosomal Protein L11; RPL23: Ribosomal Protein L23; RPL5: Ribosomal Protein L5; RPS7: Ribosomal Protein S7; AMPK: AMP-activated Protein Kinase; TSC2: Tuberous Sclerosis 2; mTOR: Mammalian Target of Rapamycin; NF-Y: Nuclear Transcription Factor Y; p300: E1A Binding Protein p300; EGR1: Early Growth Response 1; p63: Tumor Protein 63; p73: Tumor Protein 73; Sp1: Specificity Protein 1; ANKRD11: Ankyrin Repeat Domain 11 gene; VDR: Vitamin D Receptor; SMAD2: SMAD Family Member 2; NRD1: Nardilysin (N-Arginine Dibasic Convertase); EFEMP2: EGF-containing Fibulin-like Extracellular Matrix Protein 2; TOP1: Topoisomerase 1; BTG2: B-cell Translocation Gene 2; MRE11: Meiotic Recombination 11; t-MDS: Therapy Related MDS; HSCT: Hematopoietic Stem Cell Transplant; NRAS: Neuroblastoma RAS; RUNX1: Runt-related Transcription Factor 1; MLL: Mixed-Lineage Leukemia; IPSS: International Prognostic Scoring System; IPSS-R: International Prognostic Scoring System Revised; SF3B1: Splicing Factor 3b Subunit 1; TET2: Tet Methylcytosine Dioxygenase 2; EZH2: Enhancer of Zeste Homolog 2; ASXL1: Additional Sex Combs Like 1; DNMT3A: DNA (cytosine-5-)-methyltransferase 3 Alpha; IDH1/2: Isocitrate Dehydrogenase 1/2; RPS14: Ribosomal Protein S14; CLL: Chronic Lymphocytic Leukemia

Introduction

Tumor Protein 53 (p53) expressed from a gene *TP53*, located on the short arm of chromosome 17, is one of the seminal tumor suppressors. While germ line mutations of p53 result in a cancer predisposition syndrome, known as Li-Fraumeni Syndrome, somatic mutations have been described in as many as 50% of all cancers underscoring its role in tumor development [1-3]. Cellular functions of p53 under normal conditions are not clear as there are very low levels of p53 under normal conditions, but p53 levels increase under stress suggesting that it protects the cells from stress. Given the central role played by p53 in protecting the cells from stress and tumor development, the majority of clinical studies have explored the diagnostic and prognostic benefits of p53. In this review, we will discuss the regulation of p53, its activation under various stress conditions and inactivation due to mutations or aberrant expression, and implications of p53 mutations in pre-malignant cancer known as myelodysplastic syndromes (MDS).

The p53 auto-regulatory loop

As noted earlier, p53 levels are minimal under normal conditions and increase upon stress. The steady state levels of p53 under normal conditions are largely dependent on the protein Mouse Double Minute 2 homolog (MDM2) through an auto-regulatory feedback loop (Figure 1). P53 is able to induce transcription of MDM2 by binding to specific DNA elements on the MDM2 promoter region and the MDM2 protein then binds and effectively inactivates p53 [4]. MDM2 reduces p53 levels by its ability to act as an E3 ubiquitin ligase to ubiquitinate p53 and signaling it to the proteasome for degradation (Figure 1).

Various forms of cellular stress, discussed below, create an imbalance in p53 auto-regulatory loop resulting in increased levels of p53 (Figure 2). The mechanism of p53 activation is unique for each type of stress but in any case p53 is modified via post-translational modifications such as phosphorylation or acetylation. These modifications limit the interaction between MDM2 and p53, inhibiting MDM2's ability to ubiquitinate p53, and thus preventing degradation of p53 [5,6].

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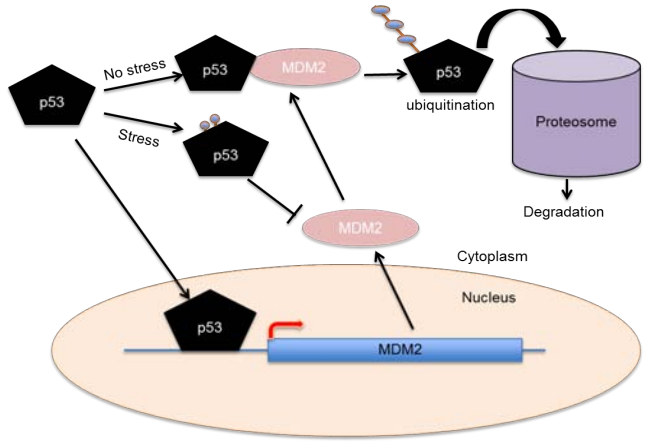

Figure 1: Regulation of p53 by MDM2. In the absence of stress, MDM2 bind and ubiquitinate p53 which is then degraded via proteasome mediated degradation. Phosphorylated p53, under stress, cannot bind MDM2 and is spared from degradation resulting in increased levels. The auto regulatory feedback loop, in which p53 binds MDM2 promoter which results in MDM2 expression and subsequent degradation of p53 keeps low p53 levels in the cells.

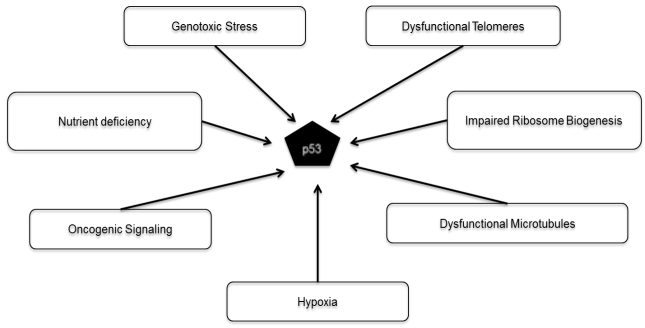

Figure 2: Modes of Activation of p53. There are a wide variety of ways to activate p53 such as genotoxic stress, malfunctioning telomeres or microtubules, nutrient deficiency, hypoxia, impaired ribosome biogenesis, as well as oncogenic signaling.

Activation of p53 upon genotoxic stress

Cells are under a routine onslaught of various agents that damage the DNA; therefore, cells have several mechanisms to repair that damage. Before every cell division, each cell checks the integrity of its genome and p53 plays a central role in this process, hence p53 is also known as "the guardian of the genome." P53 inhibits cell division if the DNA damage is not repaired [7]. Jamaa et al. study found that exposure of murine embryonic fibroblasts to DNA damage led to the activation the Ataxia Telangiectasia-Mutated (ATM)/ATM-Rad3-Related (ATR) pathway. Shortly after DNA damage, double-strand breaks are detected by an important sensor, ATM which is a member of the Phosphoinositide 3-kinase (PI3K)-like kinase family which is recruited by the MRE11-Rad50-Nbs1 (MRN) complex. ATM phosphorylates the Check Point Kinase 2 (CHK2) which then phosphorylates p53. This phosphorylation induces p53 to arrest the cell cycle [8]. A few genes that are activated by p53 include those that encode cyclin-E and A-dependent kinase inhibitor, $p21^{Cip1}$, as well as triggering a transcriptional response with p53 [9].

P53 is able to induce cell cycle arrest through the transactivation of $p21^{waf1/cip1}$, a cyclin-dependent kinase inhibitor in the G1 phase [10,11]. Cyclins, a family of proteins, are known to play a role in determining a cell's progress through the cell cycle by activating Cyclin-Dependent Kinase (CDK) enzymes. By inhibiting cyclin-CDK complexes, p53 is able to block the mechanism by which cells enter the cell cycle. This cell cycle arrest provides more time to increase DNA repair efficiency as well as perhaps activating repair genes [7]. In addition, previous studies have shown that p53 plays a role in inducing G2/mitosis arrest. The progression from G2 to mitosis is controlled by the Maturation-Promoting Factor (MPF), which is made up of a cyclin B1 and Cell Division Cell 2 (CDC2) complex. P53 is able to disrupt the cyclin B1/CDC2 complex and therefore induce a G2/mitosis arrest. Moreover, p53 is able to inhibit a phosphatase, Cell Division Cell 25 C (CDC25C), which is a key factor able to promote mitosis following DNA damage. Lastly, p53 is able to prevent effective nuclear localization of the cyclin B1/CDC2 complex following the DNA damage by transcriptionally activating 14-3-3 σ [11].

The MDM2 gene is amplified in cases of osteosarcomas and soft tissue sarcomas [12,13]. Considering MDM2's role in inhibiting p53, it is no surprise that amplification of the MDM2 gene leads to tumor growth.

Activation of p53 through dysfunctional telomeres

It has also been shown that the *TP53* gene can be activated through abnormally structured telomeres [14,15]. Telomeres play an important role in protecting the ends of chromosomes from degradation during DNA replication. The maintenance of telomeres requires telomerase, reverse transcriptase, and telomere-associated proteins. In most individuals telomerase activity is relatively low and as a result telomeres shorten with each cell division. At a critical point, the length of the telomere induces cellular senescence, through a pathway involving retinoblastoma protein (Rb) and p53. P53 plays a crucial role in the cellular response to telomere dysfunction. Telomere Repeat-binding Factor 2 (TRF2), a telomere specific protein, has been implicated in a pathway regulating p53; in fact, removing TRF2 has been found to directly activate the p53 pathway, suggesting that aberrations in telomeric structure and associated proteins are able to activate p53 [15].

Activation of p53 through oncogenic signaling

An additional mechanism by which p53 is activated is through oncogenic signaling [9,16].

The Alternate Reading Frame (ARF) tumor-suppressor protein, Alternate Reading Frame Protein 14 ($P14^{ARF}$), regulates MDM2. ARF is able to localize MDM2 in the nucleolus as well as inhibit MDM2's E3 ubiquitin protein ligase activity. ARF is induced by oncogenes such as Avian Myelocytomatosis Viral Oncogene Homolog (Myc), adenovirus E1A, and mutated Rat Sarcoma viral Oncogene Homolog (Ras), suggesting that there is a mechanism by which p53 is activated, through ARF, following significant oncogenic signaling. However, if ARF or p53 are non-functional then oncogenes are able to drive uncontrolled cell growth, leading to tumor formation [9].

Activation of p53 through dysfunctional microtubules

Microtubule malfunctioning is another path by which p53 can be activated. Microtubules are filamentous structures involved in various cellular processes including their role in chromosome

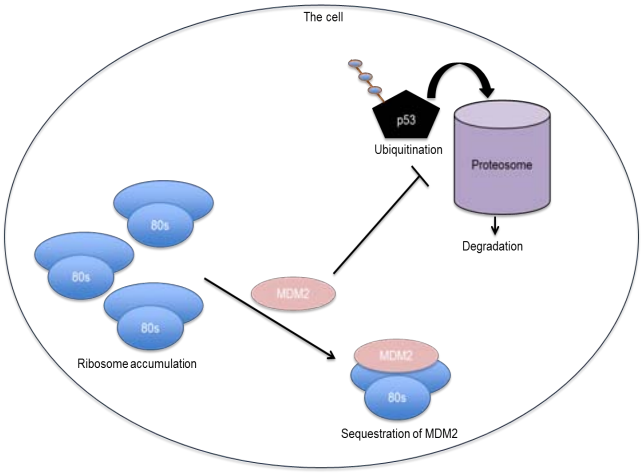

Figure 3: Ribosome Biogenesis Deregulation Leads to p53 Protein Stabilization. Deregulation of ribosome biogenesis leads to an accumulation of ribosomes in the cell. These ribosomes can then bind MDM2 and sequester it. MDM2 is a protein that plays a role in regulating levels of p53 in the cell. In normal conditions, MDM2 by tags p53 for ubiquitination and subsequent degradation in the proteosome. However, when ribosome biogenesis is deregulated, MDM2 is bound to ribosomes and sequestered leading to stabilization of the p53 protein in the cell.

segregation during mitosis by forming mitotic spindles. Recent studies have shown that p53 induces cell cycle arrest if microtubule formations are dysfunctional. It is possible that hyperploidy, caused by dysfunctional spindle formations, may induce a cell cycle arrest because the G1 cells would have a 4N DNA content. An additional theory is that the dysfunctional spindles may somehow cause DNA damage, and thus signal the p53 pathway [17].

Activation of p53 by impaired ribosome biogenesis

Ribosome biogenesis is a highly coordinated process that begins in the nucleolus and ends in the cytoplasm. Although the exact mechanism by which impaired ribosome biogenesis leads to p53 activation is still unknown, it is clear that nucleolar stress triggers a p53 signaling pathway allowing the cell to monitor ribosomal integrity (Figure 3). This nucleolar stress, which could be due to ribosomal mutations or deficiency, results in the release of free ribosomal proteins or accessory factors into the nucleoplasm where they bind and sequester MDM2, resulting in the activation and stabilization of p53. Currently four ribosomal proteins are known to have a high affinity for MDM2, and play a role in its regulation: Ribosomal Protein L11 (RPL11), Ribosomal Protein L23 (RPL23), Ribosomal Protein L5 (RPL5), and Ribosomal Protein S7 (RPS7); however any ribosomal protein deficiency has the potential to induce nucleolar stress leading to the activation of p53. The activation of p53 by nucleolar stress causes cell cycle arrest and apoptosis [18].

Additional modes of activation

In response to glucose starvation and nutrient deficiency, AMP-activated Protein Kinase (AMPK) activates p53. Moreover, the nutrient deficiency also leads to the inhibition of AKT, which assists in activating MDM2, a regulatory protein of p53. Following activation, p53 induces expression of Tuberous Sclerosis 2 (TSC2), which then leads to the inhibition of Mammalian Target of Rapamycin (mTOR), which plays an important role in protein synthesis and suppresses the induction of autophagy. Ultimately nutrient deficiency leads to a decrease in cell growth as well as p53-mediated activation of autophagy [19].

Low oxygen tension, or hypoxia can lead to activation of p53 by the ATR-Check Point Kinase 1(CHK1) kinase cascade. Specifically hypoxia activates ATR and then CHK1, which have both been shown to associate and stabilize p53 during hypoxia. ATR appears to phosphorylate p53 and thus activate it in response to hypoxia. In addition, CHK1 seems to phosphorylate MDM2 thus leading to p53 stabilization [20].

Somatic mutations in TP53 in cancers

Somatic mutations in the *TP53* gene are described in almost all types of cancers. A majority of the mutations described in the *TP53* gene cluster in the DNA binding domain between codon 125 and 300 [21]. Studies have shown that 74% of the mutations present in a mutant *TP53* gene are missense [22]. The most common mutations are in one of these regions: R175, G245, R248, R249, R273 and R282. Within the missense mutations, the largest number of missense mutations (>7.5% each) occur at amino acid positions 248 and 273 [23]. The majority of the mutations in p53 affect either its structure or its ability to bind DNA resulting in an impact on p53 transcriptional activities thus affecting a repertoire of genes activated by p53. Moreover the mutant p53, in some cases, is no longer regulated by the MDM2 protein. While the wild-type p53 protein has a relatively short life, the mutant p53 proteins are able to last longer, due to a conformational change that no longer allow binding, ubiquitination, and subsequent degradation by MDM2, and therefore the mutant p53 proteins are able to drastically enhance their tumorigenic capabilities [24,25].

Mutations in the *TP53* gene can lead to either loss of function, a lack of expression of p53 or production of an unstable mutant protein, and gain of function mutant p53, which can enhance tumor growth by binding and activating growth-related transcription factors and binding and inhibiting tumor suppressors [26]. After examining the functions of p53, it is no surprise that it is a pivotal gene for the inhibition of tumor growth. In fact, multiple studies have shown that both mice and humans lacking or expressing a mutant p53 are far more likely to initiate tumorigenesis [27-30].

Gain-of-function mutations in p53

While a majority of the mutations in the *TP53* gene results in the loss of function, there are multiple ways that gain of function mutant p53 can affect transcription and other non-transcription proteins to promote tumor growth. For example, mutant p53 has been found to recruit the cofactor E1A Binding Protein p300 (p300) and form a triple complex with Nuclear Transcription Factor Y (NF-Y), leading to histone acetylation, and upregulation of cyclin A, cyclin B1, CDK1, and CDC25C, as well as the CDK1-associated kinase activities [31]. Moreover mutant p53 has been found to physically bind to the promoter and enhance transcription of the Early Growth Response 1 (*EGR1)* gene, which encodes a transcription factor associated with cellular resistance to apoptosis [32].

Mutant p53 also has ways to inhibit transcription. Mutant p53 can bind to transcription factors, proteins, and cofactors, such as Tumor Protein p63 (p63), Tumor Protein p73 (p73), Specificity Protein 1

(Sp1), p300, Ankyrin Repeat Domain 11 (ANKRD11), Vitamin D Receptor (VDR), SMAD Family Member 2 (SMAD2), blocking the transcription factors from binding to the DNA and thus preventing transcription of their target genes. Many of the known proteins that mutant p53 inhibits are tumor suppressors or have been found to enhance the activity of tumor suppressors.

For example, p63 and p73 are part of a family of transcription factors, including p53. P63 is involved in the development of epithelial cells and is considered a tumor suppressor. Mutant p53 has been implicated to form a complex with p63 and p73 inhibiting their tumor suppressor abilities or inactivating their abilities to bind to DNA and act as transcription factors [33,34].

Lastly, p53 has been known to interact with proteins which are not involved directly with transcription, such as Nardilysin (N-Arginine Dibasic Convertase) (NRD1), EGF-containing Fibulin-like Extracellular Matrix Protein 2 (EFEMP2), Topoisomerase 1 (TOP1), B-cell Translocation Gene 2 (BTG2), and Meiotic Recombination 11 (MRE11), and either enhances or blocks their function. In one instance, a subset of mutant p53 is able to bind NRD1 and promote an invasive response to heparin binding-epidermal growth factor-like growth factor, leading to increased tumor growth [35].

Myelodysplastic syndrome and its progression to acute myeloid leukemia

Myelodysplastic syndromes, or MDS, are a heterogeneous group of clonal hematopoietic disorders that predominate in the elderly and are characterized by dysplastic bone marrow morphology, variable cytopenias in the presence of a hypercellular marrow [36]. No accurate figures for incidence and prevalence of MDS are available but estimates of incidence range from 12,000 to 40,000 new cases and estimates of prevalence range from 60,000 to 170,000 persons living with MDS in the United States [37,38]. MDS is a premalignant condition and less than one third of the patients transition to secondary Acute Myeloid Leukemia (AML), which is a universally fatal illness [39]. According to the World Health Organization criteria, the diagnosis of AML requires at least 20% of the bone marrow cells to be blasts of myeloid origin [40].

While majority of the MDS cases are de novo, MDS arise in patients who were earlier treated with alkylating agents. This type of MDS is termed as therapy related MDS (tMDS) [41,42]. This disorder typically appears roughly 4-7 years after the therapy [43]. Approximately two thirds of the cases present with t-MDS while the other one third presents with t-AML. In general t-MDS and t-AML have a poor clinical outcome [44]. Moreover there seems to be a correlation between the fact that these patients received some sort of therapy treatment and a presence of chromosomal abnormality, specifically aberrations on chromosomes 5 and 7 [45].

MDS represent a disease with serious unmet needs in the area of diagnosis, prognosis and therapy. The only curative option for MDS patients is hematopoietic stem cell transplant (HSCT), which is not an option in many MDS patients due to their advanced age.

TP53 mutations in myelodysplastic syndrome

TP53, along with Neuroblastoma RAS (*NRAS)* and Runt-related transcription factor 1 (*RUNX1)*, were among the first few genes to be screened for mutations in patients with MDS and secondary AML [46-60]. Although mutations were found in these genes in a subset of MDS patients the incidence and prognostic information could be not be reliably calculated due to small sample size and limited survival data. The recent advances in mutations detection techniques and sequencing technologies enabled a large scale sequencing of hundreds of MDS patients resulting in a genomic landscape and frequent alterations in MDS [42,61-64]. The genomic landscape of MDS, like other myeloid malignancies, is different than solid tumors [63]. The genes frequently mutated in MDS are involved in mRNA splicing or epigenetic modifications [63]. Unlike solid tumors, in which the rate of *TP53* mutations ranges from 38 to 50%, *TP53* mutations in MDS are less than 10% [42,64,65] But in tMDS patients or MDS patients who were exposed to radiation, like atomic bomb survivors, the rate of *TP53* mutations is higher ranging from 27% up to 86%.[42,66] A subset of tMDS cases with Mixed-Lineage Leukemia (MLL) gene amplification also showed a high frequency of mutations in *TP53* gene [67-69]. Like in other cancers, a majority of the mutations were missense and were located in the DNA binding domain without any apparent clustering around the common hotspots [42]. Mutations in *TP53* were infrequent in patients with mutations in splicing factors [42].

Considering p53's notoriety in the cancer field as a whole, it comes as no surprise that p53 is similarly a pivotal gene for understanding MDS. Although the exact mechanism for how mutant p53 affects transcription and protein interactions is unknown, it is likely through similar mechanisms such as the ones elucidated earlier in the review.

Prognostic implications of TP53 Mutations

One of the most challenging issues in MDS has been the development of an accurate prognostic classification system. Prognosis information is an essential part of clinical care in MDS. International Prognostic Scoring System (IPSS) and most recently the revised International Prognostic Scoring System (IPSS-R) are the most popular prognostic systems currently being used to assess a patient's survival and likelihood of transition to AML [70]. Both systems rely on cytopenias, blast counts, and cytogenetics but lack incorporation of specific molecular abnormalities. Recent studies assessing the role of gene mutations and their contribution to prognosis found that mutations in some genes, like Splicing Factor 3b Subunit 1 (*SF3B1)*, Tet Methylcytosine Dioxygenase 2 (*TET2)*, Enhancer of Zeste Homolog 2 (*EZH2)*, Additional Sex Combs Like 1 (*ASXL1)*, DNA (cytosine-5-)-methyltransferase 3 Alpha (*DNMT3A)*, Isocitrate Dehydrogenase 1/2 (*IDH1/2)* and *TP53* can be used as an independent prognostic indicator of survival in MDS [64,71-75].

Typically a complex karyotype (>3 abnormalities) receives a higher score, and hence a higher calculated risk of AML, in both IPSS and IPSS-R and is associated with reduced overall survival. However, the molecular genetic analysis of *TP53* mutations in this subset found that patients with complex karyotype but no *TP53* mutations show a survival comparable to patients without multiple karyotypic abnormalities [64]. Alternatively, patients with normal karyotype who typically receive a lower score and hence lower risk of AML in both IPSS and IPSS-R, if found to have a *TP53* mutations show poor survival [76]. Both these observation underscore the importance of including molecular genetic information in prognostication and the association of *TP53* with poor survival [64]. In general, mutations in the *TP53* region are associated with a poor prognosis and can be used

Table 1: Median survival of various subgroups of MDS patients with or without mutations in *TP53* gene.

References	Subgroup	Median Survival	
		TP53 Mutation (+)	TP53 Mutation (-)
Bejar, R. et al. (Reference 64)	High/ Intermediate-2 MDS	6 months	18 months
	Complex Karyotype	12 months	45 months
Bejar, R. et al. (Reference 76)	Lower Risk (Low Risk/ Intermediate-1) MDS	18 months	28 months
Volkert, S. et al. (Reference 82)	All	12 months	No Median
	Del(5q) MDS	13 months	N/A
Jadersten, M. et al. (Reference 84)	Low Risk Del(5q) MDS	60 months	72 months

Note: "No Median" refers to survival curves in which there was no median data. Moreover N/A refers to a lack of survival curve. In general MDS patients with *TP53* mutations have a reduced median survival compared to patients without a *TP53* mutation.

as an independent prognostic indicator (Table 1). Mutations in *TP53* were more prevalent with complex karyotypes [42,64]. For example in Bejar et al. study, it was found that eight out of the 33 mutant samples had abnormalities on chromosome 17 suggesting that mutations and chromosomal aberrations are frequently found together, thus eliminating the activity of wild type *TP53*. Moreover in the study it was reported that *TP53* gene mutations were found more commonly in patients with intermediate-2 or high-risk disease according to the IPSS. In addition Bejar et al. reported that somatic mutations in *TP53* are associated with certain cytopenias, like thrombocytopenia, and elevated blast percentage. In summary, presence of a mutation in *TP53* gene has been associated with a dramatic increase in transformation of MDS to AML; studies have shown the increased risk of transition to exist both in mice and in humans [77,78].

TP53 mutations and isolated deletion 5q

5q- syndrome represents a distinct subgroup of MDS characterized by deletion of the long arm of chromosome 5 as the sole cytogenetic abnormality, along with macrocytic anemia, a normal or increased platelet count, hypolobular megakaryoctyes and low blast count (<5%) [44]. An isolated del(5q), even in the absence of the syndrome, is associated generally with a good prognosis, although often patients with this deletion require many blood transfusion [79]. The median survival of patients with an isolated del(5q) is 145 months [80]. Furthermore, an isolated del(5q) has a much lower chance of transitioning to AML than other cytogenetic abnormalities [81]. Several studies found that *TP53* mutations were strongly associated with isolated del(5q) [42,82]. Unfortunately patients who have an isolated del(5q) have a much worse prognosis if associated with mutations in *TP53* [83]. It appears that the overwhelming negative effects of a mutation in the p53 region negate the positive prognosis associated with an isolated del(5q). The molecular basis for the higher association of *TP53* mutations with 5q- is not clear [42,84].

TP53 mutations and response to therapy in MDS

Allogenic hematopoietic stem/progenitor transplant is the only potentially curative option for MDS patients but because of the advanced age at diagnosis (median 71 years) this remains an option for very few patients. Currently there are three FDA approved disease modifying drugs in use in MDS patients and this include Lenalidomide (Revlimid), 5-azacytidine (Vidaza), and 5-aza-2'-deoxycytidine or decitabine (Dacogen) but many patients fail to respond to these drugs and those who initially respond for few months to years eventually stop responding. Several studies assessed the relationship between *TP53* mutation status and response to chemotherapy to above agents. A study of 62 patients with high risk MDS or AML treated with Azacitidine found that TP53 mutations had no significant impact on response to Azacitidine [85].

Another study assessed the relationship of *TP53* R72P polymorphism with response to lenalidomide and found that the response duration increased proportionate to C-allele dosage in del(5q) patients [86]. Wattel *et al*. assessed association between *TP53* mutations and response to Ara C and found that p53 mutations were associated with resistance to chemotherapy and short survival in MDS, AML and Chronic Lymphocytic Leukemia (CLL) patients. They hypothesized that p53 mutations could induce drug resistance, at least in part, by interfering with normal apoptotic pathways in tumor cells [54].

In addition, it appears that patients with mutations in the TP53 region are particularly resistant to chemotherapy and, in general, have remarkably decreased survival [54]. Recent data also suggest that presence of TP53 mutations predicts a poor outcome and a high likelihood of relapse and death after Hematopoietic Stem Cell Transplant (HSCT) [87,88]. It has been shown that del (5q) MDS patients have ribosomal deregulation, leading to aberrant expression of p53. However, lenalidomide has been shown to restore the MDM2 functionality which in turn accelerates degradation of p53 [89].

Expression of p53

It has been found that determining the expression of p53 through immunohistochemical analysis can be a very useful indicator of disease progression and future treatment choices [90]. One study, analyzed p53 expression of 85 del(5q) MDS patients treated with lenalidomide. This study, using immunohistochemistry, found that patients with a strong p53 expression were significantly associated with a higher incidence of transition to AML, shorter survival, and lower cytogenetic response rate [88]. In addition, a different clinical study found that suppression of TP53 in del (5q) MDS patients showed a marked increase in erythropoiesis.

It has been determined that ribosomal protein deficiency associated with del(5q) activates p53 and causes aberrant expression, which in turn leads to hypoplastic anemia. However, the study determined that cleaving TP53, and thus down regulating p53 expression can restore normal p53 expression and erythropoiesis. This study suggests that lenalidomide resistant del(5q) MDS patients can be treated by rescuing normal p53 expression [91].

Another study sought to determine whether Azacitidine response is affected by p53 expression. This study analyzed 100 higher-risk MDS patients who completed at least one cycle of Azacitidine and found that p53-mutated patients had an improved overall response rate compared to p53-wild-type patients and that response to Azacitidine was independent of p53 expression [92].

Conclusion

It is clear that a deeper understanding of genetic mutations is necessary to accurately assess an MDS patient's survival and general prognosis. P53 is a tumor suppressor that, if inhibited, can overwhelm positive prognoses and result in a dismal outcome. It is therefore important for any classification system to take into account those mutations in genes which are critical in cancer regulation, such as *TP53*, when assessing a patient's prognosis.

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