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Review Article

Progress in deciphering the role of p53 in diffuse large B-cell lymphoma: mechanisms and therapeutic targets

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Abstract: Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, accounting for 30%-40% of non-Hodgkin lymphoma in adults. The mechanisms underlying DLBCL occurrence are extremely complex, and involve the B-cell receptor (BCR) and Toll-like receptor (TLR) signaling pathways, as well as genetic abnormalities and other factors. With the development of high-throughput sequencing, an increasing number of abnormal genes have been identified in DLBCL. Among them, the tumor protein p53 (*TP53*/p53) gene is important in DLBCL occurrence. Patients with DLBCL carrying *TP53* gene abnormalities generally have poor prognosis and studies of p53 have potential to provide a better basis for their treatment. Normally, p53 is maintained at low levels through its interaction with murine double minute 2 (MDM2), and prevents tumorigenesis by mediating cell cycle arrest, apoptosis, and repair of damaged cells, among other processes. Therefore, the prognosis of patients with DLBCL harboring *TP53* gene abnormalities (mutations, deletions, etc.) is poor, and targeting p53 for tumor therapy has become a research hotspot, following developments in molecular biology technologies. Current treatments targeting p53 mainly act by restoring the function or promoting degradation of mutant p53, and enhancing wild-type p53 protein stability and activity. Based on the current status of p53 research, exploration of existing therapeutic methods to improve the prognosis of patients with DLBCL with *TP53* abnormalities is warranted.

Keywords: Diffuse large B-cell lymphoma (DLBCL), *TP53*/p53 gene (tumor protein p53), p53 mutant, murine double minute 2 (MDM2), targeted therapy

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous hematologic malignancy, and the most common non-Hodgkin lymphoma (NHL) type in the World Health Organization classification, comprising approximately 30%-40% of NHL in adults [1]. Although many patients with DLBCL can be cured using the R-CHOP (rituximab, a humanized monoclonal CD20 antibody plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone) regimen as first-line treatment, around 10%-15% exhibit primary refractory disease and a further 20%-25% patients relapse, usually within the first 2 years [2-5]. Existing salvage chemotherapy regimens, combined with autologous hematopoietic stem cell transplantation, can only cure approximately 10% of patients with relapsed/refractory (R/R) DLBCL [6-8].

Abnormalities of the tumor protein p53 (*TP53*/p53) gene and dysregulation of p53 pathways are important reasons underlying the development of various malignancies. Deletion of *TP53* is detected in 8%-24% of DLBCL, and around 20% of DLBCL tumors have *TP53* gene mutations. Thus, p53 pathway inactivation has an important role in DLBCL development. Many scholars have investigated the mechanisms involved in p53 activity in DLBCL. For example, Lu et al. elaborated the mechanism underlying *TP53* gene function in the context of DLBCL from several perspectives, including the involvement of microRNA (miRNA), copy number alterations, p53 deficiency, and MDM2, among others [9]. Further, different aspects of p53 activity, including RNA levels, protein structure, and protein stability, were summarized by Xu-Monette et al. [10]. The general consensus of studies to date is that patients with DLBCL with p53 gene

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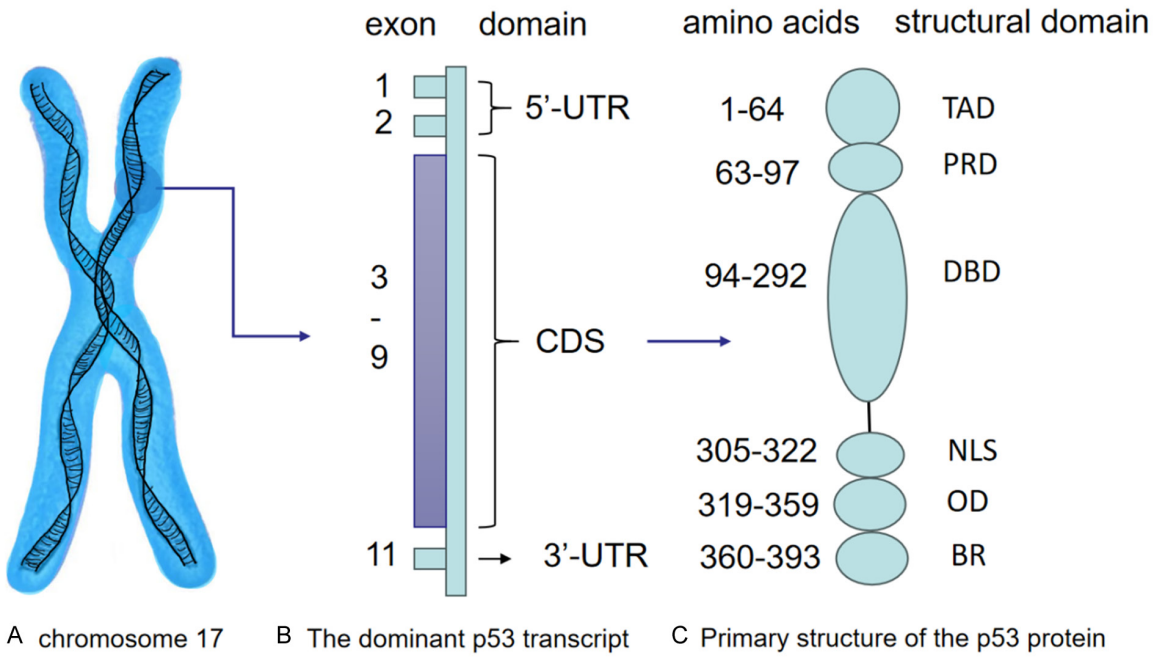

Figure 1. A. The *TP53* gene is located on chromosome 17p13.1. B. The dominant *TP53* transcript includes 11 exons, divided into untranslated region (UTR) and coding sequence (CDS). C. p53 protein domains include an N-terminal transactivation domain (TAD), a proline-rich domain (PRD), a core DNA-binding domain (DBD), nuclear localization sequence (NLS), oligomerization domain (OD), and basic repression (BR) region of the DBD.

abnormalities have poor prognosis; therefore, development of methods to target the p53 pathway, by understanding the underlying mechanisms, is warranted and could help to improve DLBCL patient prognosis, underling the significance of this aspect of our study. To date, there has been a lack of specific studies into the targeting of p53 in patients with DLBCL. In this review, we summarize the latest developments in understanding of the different mechanisms involving p53 in DLBCL, as well as recent progress in therapeutic approaches targeting p53.

Structure and function of the *TP53* gene

TP53 is the most commonly mutated gene in human cancer cells, and among the most widely studied tumor suppressor genes. *TP53* is located on chromosome 17p13.1, where it spans 19,144 bp. The dominant *TP53* transcript is a 2586-nucleotide mRNA, including a 5-untranslated region (UTR) in exons 1 and 2, coding sequence (CDS) in exons 2 to 11, and a 3-UTR in exon 11 [10, 11]. The p53 protein encoded by *TP53* comprises 393 amino acids and contains multiple functional domains and motifs, including an N-terminal transactivation domain, a proline-rich domain, a core DNA-binding domain (DBD; the main target for mutations), a nuclear localization sequence, an oligomerization domain, and a basic repression region of the DBD [10, 12]. The DBD contains a central immunoglobulin-like β-sandwich scaffold, as well as a loop-sheet-helix structure and two large loops, and can bind DNA to influence transcriptional activity (**Figure 1**).

Under normal conditions, p53 maintains a dynamic balance with the murine double minute 2 (MDM2) negative feedback pathway, which promotes p53 protein degradation to maintain it at a low level [13, 14]. Wild-type p53 protein is activated when stimulated by stressors, such as carcinogenic factors, hypoxia, heat shock, and UV irradiation, among others. Activated p53 binds to specific DNA response elements and regulates downstream target genes (including *BAX*, *NOXA*, *PUMA*, *P21*, etc.) through two pathways: transcription-dependent activities (TAs) and transcription-independent activities (TIAs). TAs primarily occur in the nucleus and are activated or inhibited by p53 through direct or indirect binding to target genes. TIAs

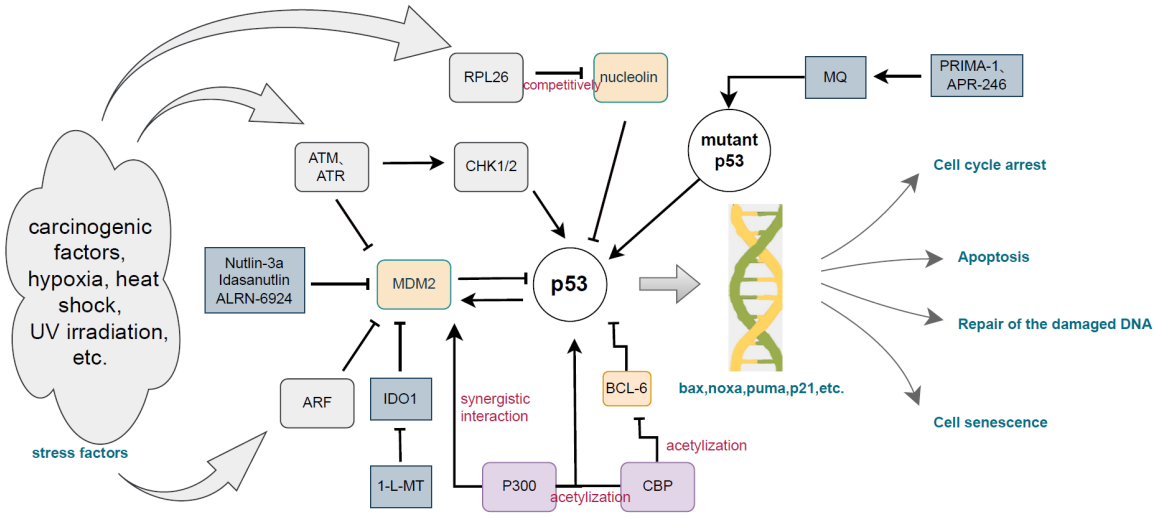

Figure 2. (1) p53 is activated when stimulated by stress factors (carcinogenic factors, hypoxia, heat shock, ultraviolet radiation, etc.). Activation signals inhibit the expression of murine double minute 2 (MDM2) via ataxia telangiectasia-mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR). Simultaneously, ATM can directly phosphorylate p53 via CHK1/2. Further, ARF can enhance p53 transcriptional activity by combating the p53 decay regulated by MDM2. Activated p53 protein induces arrest of the cell cycle in G1 phase, restoring cell function and repair cellular damage, or inducing apoptosis to eliminate damaged cells, thus avoid tumorigenesis, by regulating downstream target genes, including *BAX*, *NOXA*, *PUMA*, and *P21*, among others. (2) CREB-binding protein (CREBBP, also called CBP) and E1A-binding protein P300 (EP300, also called P300) can acetylate p53 and activate p53 transcriptional activity. P300 affects the concentration of p53 in normal cells through its synergistic interaction with MDM2. CBP can also acetylate BCL-6, reducing its activity as a transcriptional repressor, thereby increasing p53 activity. (3) PRIMA-1 and its methyl analog, APR-246, are initially converted to the active metabolite, methylene quinuclidinone (MQ), that reacts covalently with specific thiol groups of the mutant p53 protein, converting mutant p53 protein to wild-type. Moreover, MDM2 inhibitors (nutlin-3a, idasanutlin, ALRN-6924) activate p53 by disrupting the MDM2/p53 interaction. MDM2-p53 signaling is downstream of indoleamine 2,3-dioxygenase 1 (IDO1) in DLBCL. 1-Methyl-L-tryptophan (1-L-MT) can inhibit MDM2 expression by reducing IDO1 activity, thereby activating the p53 pathway and inducing p53-induced apoptosis and cell cycle arrest.

are mediated by protein-protein interactions, and associated with apoptosis via the intrinsic mitochondrial pathway and autophagy [10]. Together, these processes can induce cell cycle arrest in G1 phase, restore cell function, and allow damage to be repaired, or induce apoptosis to eliminate damaged cells, thus avoiding tumorigenesis [15-17].

The p53 protein is mainly regulated by two mechanisms in response to DNA damage. The first is in association with ataxia telangiectasia-mutated (ATM) protein phosphorylation. On DNA damage, the upstream ATM molecule suppresses expression of the p53 down-regulatory factor, MDM2, leading to p53 phosphorylation on Ser15 and extending the p53 protein half-life. Simultaneously, ATM can also directly phosphorylate p53 via CHK1/2, which greatly enhances the ability of p53 to bind target DNA (**Figure 2**) [17]. The second mechanism is independent of ATM phosphorylation. In normal cells, nucleolin binds to the 5'UTR of *TP53* mRNA, inhibiting p53 translation, and maintaining low p53 protein levels. When DNA is damaged, ribosomal protein L26 (RPL26) competitively binds to the 5'UTR of *TP53* mRNA, thereby increasing p53 protein levels [18]. Abnormalities of *TP53* inhibit cell growth and apoptosis, with cell division, proliferation, and repair reduced or even abolished, leading to accumulation of mutations in somatic cells, and eventual cancer development [10].

Mechanism underlying p53 dysfunction in DLBCL

The MDM2-p53 pathway

MDM2 is an important negative regulator of p53. Under normal circumstances, MDM2 transports p53 protein to the cytoplasm and promotes its degradation. Further, p53 can induce MDM2 expression, leading to a negative

feedback self-regulatory loop [19]. Inhibition of MDM2 and its cognate complex protein, MDMX, is the most important regulatory pathway for p53 activation. Stress signals can upregulate the expression of ATM, ataxia telangiectasia and Rad3-related (ATR), and other proteins, through sensory proteins, thereby reducing MDM2 levels [20]. MDM2 is amplified in a subset of DLBCL tumors, resulting in increased ubiquitination and degradation of p53, and decreasing its nuclear accumulation and transcriptional activity. Moreover, MDM2 binds to and transcriptionally silences p53. *TP53* mutations, MDM2 overexpression, and downregulation of p19ARF (a negative regulator of MDM2), are all important factors influencing DLBCL initiation [21, 22], with *TP53* mutations and MDM2 overexpression highly correlated in DLBCL. Møller et al. found that 23 of 37 (62%) lymphoma cases had one or more abnormalities in p53 pathway components (p53, p19ARF, and MDM2), while 9 cases (24%) had two or three gene abnormalities [22]. MDM4 is a protein that shares structural similarities with MDM2; however, unlike MDM2, which degrades p53, MDM4 inhibits p53 by binding its transcriptional activation domain. Amplifications of MDM4 are also detected in DLBCL, and may decrease p53 transcriptional activity (**Figure 2**) [7, 23].

ARF promotes MDM2 degradation and stabilizes p53, and is frequently deleted in DLBCL. Several studies have shown that ARF can enhance p53 transcriptional activity by combating MDM2-mediated p53 decay [24-26]. Proteins such as ATM and DNA-dependent protein kinase (DNA-PK) can be activated in response to DNA damage conditions, inducing p53 Ser15 phosphorylation and reducing the ability of p53 to bind to MDM2, thereby stabilizing p53 and enhancing its activity [18, 27]. Mutations in the important cell cycle checkpoint kinase, ATM, are associated with inferior progression free survival (PFS) of patients with DLBCL [28, 29].

CREB-binding protein (CREBBP, also termed CBP) and E1A-binding protein P300 (EP300, also termed P300) are two key acetyltransferases and transcriptional cofactors that regulate gene expression by controlling the acetylation levels of histone and non-histone proteins. CREBBP and EP300 can acetylate p53 and activate its transcriptional activity, while P300 affects p53 levels in normal cells through its synergistic interaction with MDM2 [30-32]. CREBBP can also acetylate BCL-6, reducing its transcriptional repression function, and thereby increasing p53 activity [21, 33]. Acetylation of p53 after DNA damage or oncogene activation may be regulated by changes in the conformation or affinity of the P300/MDM2 complex. Hence, mutations in CREBBP and EP300 inactivating the acetyltransferase activity of these two proteins, impair p53 acetylation and activity [23, 34, 35]. CREBBP mutations, include truncating and missense mutations in the histone acetyltransferase domain, have been reported in 20% of patients with DLBCL, while EP300 is mutated in 10% of DLBCLs [31, 36, 37].

p53 mutations

TP53 mutations are the most common genetic alterations detected in human tumor cells and the most frequent *TP53* mutation is located in the region encoding the p53 DBD, often occurring in exons 4-7; mutations are rarely observed in the *TP53* promoter and UTR. *TP53* mutations include missense, nonsense, and synonymous changes. Missense mutations, affecting only one amino acid, and expressed as a full-length mutant p53 protein with a single amino acid substitution, are the most common. Based on the dysfunctionality of the resulting protein, p53 mutations can be classified as DNA-contact mutations (such as R248 and R273) and conformational mutations (such as R175, G245, R282, and R249) [12, 38]. DNA-contact mutations occur in the DBD and change amino acid residues in the DNA contact surface, directly affecting their ability to control the transcription of targeted genes. Conformational mutations usually result in a more dramatic alteration of p53 protein structure than that caused by DNA-contact mutations [39]. Around 90% of p53 mutations are accompanied by loss of function. Mutant p53 protein can both lose the tumor suppressor effect of its wild-type counterpart and exhibit dominant negative regulation of residual wild-type p53 [10, 40, 41]. Alternatively, many p53 mutant proteins also acquire new activity to promote tumorigenesis independently of wild-type p53 protein, termed gain-of-function (GOF). GOF mutant p53 increases tumor malignancy in var-

ious ways, including by mediating tumor metastasis, chemoresistance, and invasiveness, and is associated with shorter patient survival [12, 15, 39].

Although *TP53* mutations are the most common gene mutations in human tumor cells, their incidence in lymphomas is relatively low (20%) [22]. Zlamalikova et al. detected 26 *TP53* mutations in 131 DLBCL cases (19.8%), 3 of which carried two p53 mutations. Of the 26 mutations, 24 were missense, and 2 were nonsense, leading to formation of a premature termination codon. All mutations were localized in the CDS [42]. Møller et al. identified 7 *TP53* mutations in 37 DLBCL cases, all of which were base substitution missense mutations affecting the conserved hotspot regions of exons 5-8, which is within the CDS, consistent with the findings of previous studies [22].

TP53 deletion

Compared with *TP53* mutation, *TP53* gene deletion has been less extensively studied. Tamimi et al. performed polymerase chain reaction amplification and sequencing of samples from 23 patients with DLBCL and found that 35% had *TP53* allele deletion [43]. A strong correlation between *TP53* point mutations and *TP53* loss is established; hence, when the *TP53* gene on one chromosome is deleted, that on the other allele is frequently mutated. Zlamalikova et al. analyzed loss of the *TP53* locus in 131 DLBCL cases and found that 20 (15.3%) had *TP53* gene deletions, with concurrent *TP53* mutations in 10 [42]. Similar to *TP53* mutations, *TP53* deletion is associated with inferior prognosis of patients with DLBCL. Jia et al. studied 50 patients with DLBCL by fluorescence in situ hybridization, and found that 40% had *TP53* gene deletions. In addition, these authors applied a Cox proportional hazards regression model to analyze factors associated with survival prognosis in all patients with DLBCL, and showed that patients with DLBCL harboring *TP53* gene deletion had poor prognosis, independent of age. The elevated proportion of *TP53* gene deletions reported in that study, relative to previously published data, may be attributable to differences in DLBCL patient samples and detection techniques [44].

MiRNA and p53

MiRNAs are highly conserved, non-coding, single-stranded RNA molecules which occur widely in eukaryotes and comprise 18-23 nucleotides. MiRNAs can recognize binding sites in target gene mRNA 3'-UTRs, and function to inhibit transcription, or reduce or degrade mRNA, thus inhibiting the expression of downstream genes and weakening or eliminating their function [45, 46]. In DLBCL, miRNA can exert pro- or tumor suppressor effects through a number of known cancer-related genes. For example, miR-155, miR-17-92, and miR-21 act as oncogenes by altering the expression levels of MYC, SHIP, and FOXO1, respectively; conversely, miR-34a, mir-144, and miR-181a act as tumor suppressors by altering the expression levels of SIRT1, BCL-6, and CARD11, respectively [35, 47]. *TP53* can mediate its antitumor effects by regulating the transcription of a range of microRNA molecules. MiR-34 family members are direct targets of p53 and were the first miRNAs found to be directly regulated by p53 as a tumor suppressor. One study profiled miRNA gene expression in p53-positive and p53-deficient cells, revealing that the miR-34 family was among the most up-regulated gene families in p53-positive cells. The miR-34 family includes miR-34a, miR-34b, and miR-34c, which are encoded by two different genes. When cells are stimulated, p53 activates miR-34a expression by demethylating the CpG island in its promoter region, consequently regulating miR-34a target genes. Moreover, miR-34a activates p53 by inhibiting the c-MYC/SIRT1 pathway, which upregulates miR-34a expression, thereby causing cell cycle arrest [35, 45, 48]. MiR-34a expression is significantly lower in lymphoma than in normal lymph nodes. Similarly, miR-34a expression is low in patients with DLBCL. He et al. analyzed 58 patients with DLBCL and found that only 5 (8.6%) were miR-34a positive, and most the miR-34a-positive cases were weakly positive, with significantly lower levels than those in normal lymph nodes [49]. Further, low miR-34a expression is associated with poor prognosis in patients with DLBCL [49, 50]. In addition, in an experiment to investigate DLBCL resistance to doxorubicin, researchers observed a significant correlation between high miR-34a expression and improved overall survival (OS) by univariate Cox regression [51].

Prognosis of patients with DLBCL with an abnormal *TP53* gene

The International Prognostic Index (IPI) is an important tool used to evaluate the prognosis

of patients with of DLBCL; however, given the biological heterogeneity and complexity of DLBCL, exploration of new biomarkers with prognostic significance is of considerable interest. Research on prognostic indicators can help in exploring DLBCL pathogenesis, as well as having the potential to identify new and rational therapeutic targets for this biologically diverse disease. Most recent studies have considered both high p53 protein expression and *TP53* mutations as independent prognostic factors associated with poor survival of patients with DLBCL [21, 52-56]. In a follow-up analysis of 506 patients with DLBCL, Zijun Y. Xu-Monette et al. found that 395 DLBCL patients without *TP53* mutations had a median OS of 94.49 months, while 111 patients with *TP53* mutations had a median OS of 52.90 months, and concluded that both OS and PFS were superior in patients with DLBCL without p53 mutations than in those with p53 mutations [57]. Zlamalikova et al. found that *TP53* mutations were associated with shorter OS and PFS in patients with DLBCL treated using the R-CHOP regimen [42]. A study reported by Antonin Bouroumeau et al. found that, univariate analysis of a cohort of patients with DLBCL receiving R-CHOP as first-line treatment, showed that p53 overexpression (positive threshold, 50%) was associated with inferior prognosis. Moreover, a DLBCL subgroup with high p53 expression was associated with c-MYC overexpression and poor prognosis [2]. Qin et al. showed that BCL-2 and p53 mutations were significantly associated with poor prognosis in patients with DLBCL treated using the R-CHOP regimen, independent of IPI. Nine patients with both BCL-2 and p53 mutations had an extremely poor prognosis, with median PFS only 4 months and OS 13 months [58]. Together, these data suggest that p53 is both a valuable prognostic biomarker for DLBCL patients treated with or without R-CHOP [58-61].

Nevertheless, some studies have also found no relationship between p53 protein expression and survival. Rujirojindakul et al. performed immunohistochemical staining of samples from 108 patients with DLBCL; univariate analysis of the results revealed no significant differences in complete remission rate (CRR), OS, or disease-free survival between p53-positive (positive threshold, 50%) and -negative groups [62]. Baran et al. analyzed data from 40 patients with histologically proven diagnosis of nodal DLBCL and also concluded that p53 expression and OS were not significantly associated [63]. These differences may reflect the fact that p53 protein expression does not exactly coincide with p53 mutations. For example, p53 protein accumulation in DLBCL tissues was assessed by immunoblotting by Zlamalikova et al., who found that 15.3% of cases showed p53 protein accumulation, including 6 p53 wild-type cases; hence, the concordance rate of p53 mutations and p53 protein accumulation was 86.3% [42]. Therefore, the lack of direct correlation between p53 mutation and p53 overexpression measured by immunohistochemical approaches, and the relationship of *TP53* mutation, p53 protein, and the prognosis of patients with DLBCL requires more precise investigation.

Targeted therapy of p53 in DLBCL

Restoring the normal function of mutant p53

Mutant p53 proteins frequently accumulate at high levels in human cancers, and targeting mutant p53 sites has emerged as an attractive therapeutic strategy for tumors containing mutant p53. The main strategy for targeting mutant p53 is to restore wild-type p53 activity and deplete mutant p53 levels in cancer cells. PRIMA-1, a mutant p53 reactivator, and its methyl analog, APR-246, are initially converted to the active metabolite, methylene quinuclidinone (MQ), a Michael acceptor that reacts covalently with specific thiol groups of mutant p53 protein, converting it to wild-type [13, 15, 64]. In addition, PRIMA-1 restores unfolded wild-type p53, which can promote tumor invasion in a similar way to mutant p53 proteins. Hence, PRIMA-1 can be beneficial to patients with tumors containing either mutant or unfolded wild type p53 [39, 65]. APR-246 can restore mutant p53 transcriptional activation function, thus inducing human cancer cell apoptosis, and has shown promising results in several clinical trials [15, 66]. For example, a phase 1 clinical trial (NCT00900614) was conducted to test the safety and activity of APR-246 in R/R hematological malignancies, including 3 NHL cases (**Table 1**) [66]. Most studies to date have found that p53 mutation is associated with poor prognosis in patients with DLBCL. Hong et al. conducted a study including 2464 patients with DLBCL and concluded that p53 mutations in exon 7 were associated with poor OS, where-

Table 1. Targeted drugs related to p53

Category	Mechanism	Target	Drugs	Trials
Mutant p53 activator	Converts MQ to an active metabolite that reacts covalently with specific thiol groups of the mutant p53 protein	p53	PRIMA-1, APR-246	NCT00900614, NCT03745716, NCT04990778, NCT03072043, NCT04214860
MDM2 antagonist	Disrupts the p53-MDM2 interaction and activates p53	MDM2	RG7112	NCT00623870
			Idasanutlin	NCT02633059, NCT04029688, NCT03850535, NCT02545283, NCT02670044
			APG115	NCT04496349, NCT04275518, NCT02935907, NCT04358393
	Has affinity for both MDM2 and MDM4, and blocks their interaction with p53	MDM2, MDM4	ALRN-6924	NCT02264613, NCT02909972
XOP1 inhibitor	Inhibits the nuclear export of p53 and restores p53 nuclear localization	XPO1	Selinexor	NCT03955783, NCT06169215, NCT02835222, NCT04717700, NCT02227251
G2 phase arrest regulators	Synthetic lethal interactions with p53-deficient cancer cells	ATR	Berzosertib	NCT04802174, NCT04826341, NCT03641313
		CHK1	Prexasertib	NCT02649764, NCT03735446

as mutations in exons 5 and 6 were associated with poor PFS. These authors also applied APR-246 to treat p53-mutated DLBCL cells and a xenograft mouse model, and found that APR-246 induced p53-dependent ferro-phagocytosis of DLBCL cells with p53 missense mutations in exon 7, and ferroptosis of DLBCL cells carrying wild-type p53 and other p53 mutations [67]. Hence, APR-246 has potential as a future therapeutic approach for patients with DLBCL carrying mutant p53.

Enhancing the stability and activity of wild-type p53 protein

Disrupting the p53-MDM2 interaction impairs MDM2-mediated p53 degradation, thereby increasing p53 stability and expression. Nutlins were the first potent and selective small-molecule MDM2 antagonists identified able to inhibit the p53-MDM2 interaction, leading to p53 stabilization and p53 pathway activation [68, 69]. Nutlin-3a, the active isoform of nutlin-3, is a potent MDM2 inhibitor that disrupts the p53-MDM2 interaction and activates p53, thereby upregulating the pro-apoptotic proteins, BAX and PUMA, and inducing apoptosis in DLBCL cell lines with the translocation [23, 70]. Therapeutic experiments using nutlin-3a have been conducted in various human tumors, including nasopharyngeal carcinoma, Kaposi's sarcoma, and multiple hematological tumors [71, 72]. The response of chronic lymphocytic leukemia (CLL) to nutlin-3a depends on p53 status, and CLL cells in the early progressive CLL subgroup are particularly sensitive to nutlin-3a. Saddler et al. performed MDM2 inhibitor killing experiments on 106 CLL samples (87 without abnormal p53 and 19 with p53 sequence mutations or absent expression) and found that the mean 50% inhibitory concentration (IC50) values for CLL cases with or without p53 abnormalities were 3.55 and 22.9 μM, respectively. This finding indicates that CLL without p53 abnormalities is more sensitive to nutlin-3; however, no such studies have been conducted in DLBCL [73].

RG7112 (RO5045337) is a second-generation nutlin-3a compound with potential antitumor activity that can inhibit proteasome-mediated enzymatic degradation of p53 by preventing the MDM2-p53 interaction. This allows restoration of p53 transcriptional activity, leading to reinstatement of p53 signaling, finally inducing p53-mediated tumor cell apoptosis. Compared with nutlin-3a, RG7112 has a lower IC50 value in tumor cells and is more selective for MDM2; however, the side effects of RG7112 are prominent, including inhibition of platelet formation and gastrointestinal symptoms in patients with leukemia, which requiring caution in using RG7112 to treat hematological disorders. A phase I trial (**Table 1**) to determine the maximum tolerated dose of RG7112 in leukemia (NCT00623870) has been completed [74-77].

Idasanutlin (RG7388) is a potent and selective MDM2 antagonist that inhibits binding of MDM2 to p53 and showed significant antitumor activity in a xenograft model of DLBCL when combined with obinutuzumab and venetoclax. This three-drug combination remarkably improved the tumor-free survival of mice. Idasanutlin combined with rituximab and venetoclax has been investigated for use in treating patients with R/R DLBCL; however, the study was prematurely terminated because of the overall modest benefit achieved with the maximal tolerable dose during the escalation phase, and Phase II of the study was never initiated. No results data were generated; therefore, the trial outcomes were not reported [7, 23, 78]. A study (NCT04029688) evaluating the safety, tolerability, pharmacokinetics, and preliminary activity of idasanutlin in combination with either chemotherapy or venetoclax for treatment of pediatric and young adult participants with R/R acute leukemias or solid tumors is ongoing (**Table 1**). ALRN-6924 (sulanemadlin), an orally available peptide inhibitor, has an affinity for both MDM2 and MDM4, and blocks their interaction with p53. At high doses, ALRN-6924 exhibits on-mechanism anticancer activity in *TP53* wild-type tumor models. Further, ALRN-6924 reduced tumor cell growth and prolonged survival of acute myeloid leukemia xenograft mice. The results of a phase I trial (NCT02264613) demonstrated that ALRN-6924 was well-tolerated and had anti-tumor activity in patients with solid tumors and lymphomas bearing wild-type *TP53* (**Table 1**) [15, 79-81].

Sun et al. demonstrated that the MDM2-p53 signaling pathway is downstream of indoleamine 2,3-dioxygenase 1 (IDO1) in DLBCL, and that reducing IDO1 activity could activate the p53 pathway by inhibiting MDM2 expression, thereby inducing the p53 apoptotic pathway and cell cycle arrest. The natural substrate of IDO, L-Trp, has an analog, 1-Methyl-L-tryptophan (1-L-MT), which acts as an IDO1 inhibitor by competitively inhibiting IDO1 enzyme activity, thereby activating the p53 pathway and inducing cell cycle arrest and apoptosis to inhibit DLBCL cell growth [82]. Exportin-1 (XPO1; also known as CRM1) is a member of the importin β family of nuclear export protein receptors, which is responsible for nuclear export of tumor suppressor proteins and bioregulatory proteins, such as p53, p21, PI3K/Akt, and NF-κB, among others. The transcriptional activation activity of p53 depends on its nuclear localization, and XPO1 mediates protein nuclear export, including of p53. High XPO1 expression predicts poor prognosis for patients with DLBCL [83]. Selinexor, an XPO1 inhibitor, reduces p53 nuclear export and restores its nuclear localization, and has received approval from the US Food and Drug Administration (FDA) for use in treating R/R DLBCL after at least two lines of systemic therapy, showing an overall response rate of 28% in the SADAL trial [84-86].

Other therapeutic pathways associated with p53

In addition to direct targeting of p53, application of mutant synthetic lethal p53 genes has also become a hot topic in recent years; for example, targeting of non-coding RNA, among other approaches. The term “synthetic lethality” indicates that, while disruption of either of two genes with synthetic lethal interactions alone is permissible, complete disruption of both genes results in cell death. Therefore, developing and targeting synthetic lethal partners may become an attractive therapeutic strategy for non-modifiable genes [32]. Abnormalities of the p53 pathway prevent normal p53 function and activate signaling cascades to promote tumor progression and compensate for loss of function. Many synthetic lethal partners may be hidden in these altered pathways. Regulators of the G2 checkpoint (ATR, CHK1, MK2, Wee1) were the first identified synthetic lethal interactors in p53-deficient cancer cells. Berzosertib (M6620) is the earliest ATR inhibitor applied in a clinical trial in humans [87]. Other G2 phase arrest regulators may also act as synthetic lethal chaperones for mutant p53. Prexasertib, a CHK1 inhibitor, demonstrated antitumor activity in several models derived from high-grade serous ovarian cancer patient samples [87]. The BCL-2 selective inhibitor, APG-2575, can exert a synthetic lethal effect with the MDM2-p53 inhibitor, APG115, in DLBCL, and effectively inhibited DLBCL with high BCL-2 expression by activating the mitochondrial apoptotic pathway. APG115 restores the tumor suppressor activity of p53 by blocking the MDM2-p53 interaction. For DLBCL with wild-type p53 and high BCL-2 expression, APG-2575 had a strong synergistic effect with the

MDM2-p53 inhibitor, APG115, inducing more significant apoptosis [88].

Autophagy is a housekeeping process that controls protein and organelle quality and recycles intracellular components. Under conditions of nutritional deprivation, autophagy can maintain normal biological activities by recycling misfolded proteins and dysfunctional mitochondria as alternative resources; however, autophagy can also promote lymphoma cell survival by recycling toxic intracellular materials and inhibiting apoptosis. The autophagy pathway can reduce mutant p53 degradation, thereby promoting tumor progression [89]. The autophagy inhibitor, spautin-1, promotes molecular chaperone-mediated autophagy degradation of mutant p53 protein, and selectively induces cell death of mutant p53-expressing cancer cell lines under confluency conditions [90, 91]. Due to the complexity of autophagy pathway activation and the cardiotoxicity of spautin-1, this anticancer therapeutic strategy requires further careful evaluation.

Chimeric antigen receptor (CAR) T cells are genetically engineered to express a synthetic tumor antigen recognizing a T cell receptor (TCR) that can induce T cell-mediated antitumor effects. CAR-T therapy is a new type of precision targeted therapy, which has achieved good results in clinical tumor treatment [85, 92], and represents a significant advance in the treatment of patients with R/R DLBCL, as second-line therapy for those with refractory disease or early relapse (within 12 months) after first-line chemoimmunotherapy. Long-term remission has been reported in approximately 30%-40% of patients who received CAR-T therapy, suggesting that it has curative potential [93-95]. *TP53* gene alteration confers inferior prognosis in patients with R/R aggressive B cell NHL. The p53 tumor suppressor gene is associated with poor CAR-T response in DLBCL [96], and in DLBCL patients with p53 abnormalities, anti-CD19 and anti-CD22 chimeric antigen receptor (CAR19/22) T cell cocktail treatment alone or in combination with autologous stem cell transplantation (ASCT) resulted in higher objective response rate, CRR, PFS, and OS; this finding suggests that CAR19/22 T cell therapy is effective for treatment of R/R aggressive B-NHL with p53 alterations [97, 98]. A case report of a patient with DLBCL with P53 gene mutation who underwent CD19 CAR T cell infusion after ASCT, found that complete molecular response was achieved at +1 month and maintained without any adverse effects [99]. Hence, the combination of CAR T cell administration with ASCT represents a potential therapeutic option for patients with DLBCL harboring p53 mutations.

Conclusion

TP53 is among the most highly relevant genes associated with human tumors identified to date, and its inactivation is closely related to the occurrence of multiple tumors. Although *TP53* abnormalities are lower in DLBCL than in other tumors, they remain an important contributor to DLBCL occurrence and development. *TP53* mutations and deletions are associated with poor prognosis of patients with DLBCL, indicating that p53 is a possible therapeutic target in this disease. Drugs targeting p53 gene abnormalities mainly function via the following routes: restoring the normal function of mutant p53 protein, promoting mutant p53 protein degradation, and enhancing wild-type p53 protein stability and activity. In recent years, there has been considerable progress in the clinical success of targeting p53; for example, the targeted drug, rezatapopt (PC14586), is highly effective in treating solid tumors with p53 Y220 mutations, and the US FDA has qualified rezatapopt to treat patients with locally advanced or metastatic solid tumors with TP53 Y220C mutations for fast-track approval.

For patients with DLBCL, gene therapy targeting p53 continues to face numerous challenges. First, there are multiple types and sites of p53 mutations, and the same mutations may play different roles in different cell types. Targeted drugs may only be effective against some p53 mutations. Second, it is unclear how the different mechanisms of action underlying p53 activity in DLBCL are interconnected and whether inhibition of one of these mechanisms affects other aspects. Third, some experimental targeted drugs, such as the MDM2 inhibitor, RG7112, exhibit strong myelotoxicity, inhibit platelet formation, and have other adverse effects; hence, their application in DLBCL has greater risks compared with solid tumors. Fourth, some p53-targeting drugs, such as APR-246, have p53-independent effects, and

these also need to be considered when exploring targeted drugs. Overall, there remain considerable challenges for clinical application of p53-targeted drugs as stand-alone therapies. Therefore, in future studies, combination of p53-targeted drugs and existing treatment options can be considered, to develop improved treatments for patients with DLBCL and *TP53* gene abnormalities. Further, focus on methods to adapt appropriate drugs to specific p53 mutations and design optimal personalized treatment options for patients with p53-mutated DLBCL, is warranted.

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Disclosure of conflict of interest

None.

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