Int J Clin Exp Pathol 2013;6(7):1223-1229
www.ijcep.com /ISSN:1936-2625/IJCEP1304037

Review Article

The role of TP53 network in the pathogenesis of chronic lymphocytic leukemia

Cheng Wang[1], Xin Wang[2,3]

[1]Department of Hematology, Provincial Hospital Affiliated to Shandong University, No. 324 Jingwu Road, Jinan, Shandong 250021, P. R. China; [2]Department of Hematology, Provincial Hospital affiliated to Shandong University, Jinan, Shandong 250012, P. R. China; [3]Department of Diagnostics, Shandong University School of Medicine, Jinan, Shandong 250012, P. R. China

Received April 26, 2013; Accepted May 11, 2013; Epub June 15, 2013; Published July 1, 2013

Abstract: *TP53* is one of the most important prognostic factors in chronic lymphocytic leukemia (CLL). Modulation of microRNAs by *TP53* in CLL pathogenesis has been a hotspot. Besides, it has an intimate association with other cytogenetics and plays an important part in drug resistance of CLL. All above indicate an embedded *TP53*-centered network in CLL pathogenesis and prognosis. In this review, we focus on the *TP53*-centered network and its roles in the pathogenesis of CLL.

Keywords: TP53 network, microRNAs, chronic lymphocytic leukemia, pathogenesis

Introduction

Chronic lymphocytic leukemia (CLL) is a malignant neoplasm characterized by accumulation of monoclonal B lymphocytes that flood the hematopoietic tissues. Its clinical course is much heterogeneous and refractory cases have poor prognosis [1-3]. Among the prognostic factors, although incidence of *TP53* mutation is lower, its clinical consequences are striking. Recently, more and more evidence support that there is a *TP53* network which could involve most prognostic factors: cytogenetics, microRNAs, *IGHV* status and so on [4-6]. It plays an important role in the pathogenesis of CLL and may be an effective tool to guide our treatment. In this review, we focus this *TP53* network in CLL.

17P deletion, *TP53* mutation and P53 aberration in CLL

P53 is encoded by *TP53* gene located on 17p but 17p deletion, *TP53* mutation and p53 aberration are not identical in the network. 17p deletion occurs in 5% - 7% of untreated CLLs and in 40% - 50% of relapsed or resistant cases [7, 8]. Deletions of band 17p13.1, where *TP53* gene is located, is one of the most common [1]. Not unexpectedly, *TP53* mutation is strongly associated with 17p deletion and the concordance is as high as 80% [5]. However, in 3% to 4.5% of cases with the *TP53* mutation not coupled with 17p deletion, it still maintains its independent adverse prognostic value [7, 9-11]. It is noteworthy that progression-free survival (PFS) and overall survival (OS) for "uncoupled" group are similar with that of "coupled" group [12, 13]. Defects of the *TP53* gene in CLL are more strongly associated with aggressive phenotypes, poor clinical outcomes, and resistance to therapy with purine analogues [7]. It should also be pointed out that not all *TP53* mutations are equal: physiologically irrelevant mutations may exist, and whether the mutation occurred in the DNA biding domain or not may be critically important [14]. It suggests *TP53* mutation testing, other than 17p deletion, more suitable for evaluation of naïve CLL patients [12, 15] so that patients with *TP53* mutation be considered for alternative treatment approaches and selected for novel experimental therapies.

It is well accepted that p53, transcript factor for P21, PCNA, GADD45, BAX, NOXA, MDM2 or miR-34a etc. [8], plays a critical role in surveil-

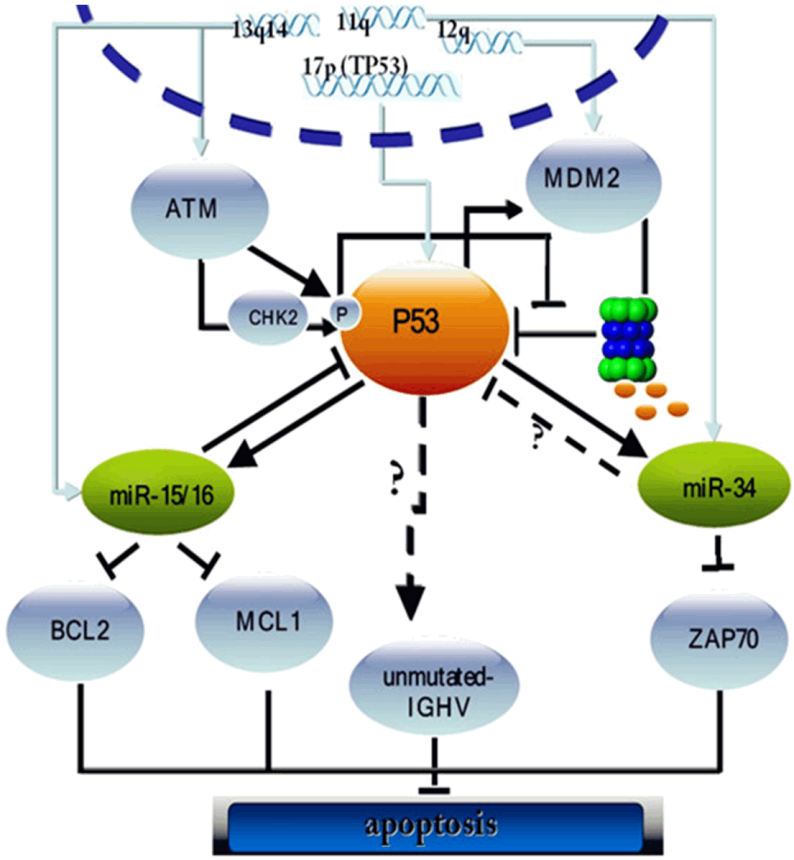

Figure 1. *TP53*-centered network in CLL: A novel pathogenetic model for chronic lymphocytic leukemia (CLL) showing a pathway of microRNAs and cytogenics that are involved in the development of CLL. *TP53* is the core molecule of this regulatory network [1, 4, 43]. Abbreviation: miR-15, microRNA 15 cluster; miR-16, microRNA 16cluster; miR-34, microRNA 34 cluster; *TP53*, genes tumor protein p53; BCL2, B-cell CLL/lymphoma 2; MCL1, myeloid cell leukemia sequence 1 (BCL2-related); ZAP70, zeta-chain (TCR)–associated protein kinase 70kDa.

lance, proliferation and apoptosis of cells. Mutated *TP53* may decrease P53 degrading sensitivity by changing its conformations [16]. However, exam of aberrant expression of p53 by Immunocytochemistry as a robust diagnostic tool for *TP53* mutation in CLL is demonstrated to be not available [10, 17]. Firstly, p53 dysfunction may exist irrespective *TP53* mutational status. p53 is only a component of a giant complex circuitry and false-positive cases will be detected due to other mechanisms [10], such as MDM2 alterations, ATM mutations, hypermethylation of *TP53* promoter and polymorphisms of BCL-2 family promoters [8]. Secondly, *TP53* abnormalities may produce physiologically normal P53 protein: wild-type on the remaining allele functions as a dominant protective mechanism [11, 16]; nonsense or microdeletion won't cause dysfunction [16]. In these situations false-negative results come out and its clinical impact is more relevant. What's more, available antibodies only can detect part of p53 isoforms [16, 18, 19]. Conclusively, the partial overlap between *TP53* and P53 in CLL indicates that there must be redundant or cooperating pathways in this *TP53* network. Besides, the prognostic value of *TP53* mutations and P53 dysfunctions have both been demonstrated [8, 9, 11], but similar to 17p deletion and *TP53* mutation, which one is more independent and decisive? To answer this question, epidemic research is necessary. Besides, recently autoantibodies against p53 protein are found in some cases with abnormalities in the *TP53* gene [20] and this may be explained by induction of P53 overexpression. In many autoimmune diseases such as dermatomyositis/polymyositis, juvenile rheumatoid arthritis and systemic lupus erythematosus, anti-p53 is at a high level [21]. Could anti-p53 be linked with other clinical characters of CLL such as autoimmune disease, secondary tumor and even drug resistance? At this point, we need more evidence.

TP53: core of the regulatory network in CLL

Abnormalities on chromosome 11, 13 and trisomy 12 are the most common in CLL and they participate in the construction of *TP53*-microRNA circuitry where *TP53* plays an essential role. In this network, microRNAs act as not only on/off switch but also fine tune pathways to these proteins [22]. Determination of interactions between *TP53* and microRNAs has led not only to the identification of novel prognostic markers but also yields new insights into its pathophysiology and provides means to overcome *TP53*-mutation associated chemoresistance in CLL [6, 23-25] (**Figure 1**).

11q

It is generally accepted that CLL *TP53* mutation is strongly associated with 11q deletion. The miR-34b (GenBank 407041)/miR-34c (GenBank 407042) are coded on 11q23 and miR-34a (GenBank 407040) on 1p36 [4, 26]. Overexpression of miR-34 family in oncology has been demonstrated as tumor suppressor with studies in a variety of cancers including colon cancer, lung caner, osteosarcoma etc. [27, 28]. It has been described as a considerably important target of the p53 protein mainly based on the following facts: p53 respectively binds to the promoter of miR-34 family and enhance their expression which could be damaged by chromosomal aberrations; miR-34 family can almost recapitulate elements of p53 activity, including induction of cell-cycle arrest and promotion of apoptosis and it is even considered as ideal target in p53 functional assays [8]; an active p53 pathway is necessary for effects of miR-34 family [29-31]. In CLL, miR-34b and miR-34c are generally absent irrespective of 11q deletion while miR-34a is severely increased in cases with intact p53 and down-regulated in cases with *TP53* abnormalities [31, 32]. In accordance with this, low expression of miR-34a in CLL is significantly associated with worse progression and chemotherapy resistance [31, 33]. Intriguingly down-regulated miR-34a is brought to light in CLL with MDM2 promoter SNP309G, suggesting possible attenuation of the p53 pathway by the SNP309G [31]. Given that microRNAs mainly regulate protein expression by binding to their 3'-UTR region, miR-34a may also target upstream p53 in turn. But which means it acts through to achieve the feedback is still unknown. SIRT1, a NAD dependent deacetylase which could inactivate p53, has been shown to be suppressed in miR-3a overexpressing HCT-116 cell line [31]. Moreover, what factors act downstream of miR-34 family is another important question. In open reading frame of to zeta-chain (TCR)–associated protein kinase 70kDa (ZAP70), one of the negative prognostic factors in CLL, a miR-34 family binding site was detected [8, 34, 35]. Other cell survival and cycle-related factors downstream may include BCL2, TCL1, MCL1, CDK etc. [4, 26, 30]. In the future blockage of miR-34 family may be a novel therapy for chemoresistant CLL patients with *TP53* mutation.

Studies on 11q deletions in CLL reveal a most affected minimal consensus region in chromosome bands 11q22.3–q23.1 which covers the gene coding ATM [1]. Under the regulation by oncogenic factors and some cytokines such as Mcl-1 ubiquitin ligase E3, the ATM-p53 pathway suppresses tumorigenesis by mediating cellular responses to DNA double-strand breaks (DSBs) and aneuploidy [26, 36, 37]. Generally, ATM maintains DNA ends in repair complexes during lymphocyte antigen receptor gene assembly [38]. When activated by oncogenic stress, ATM directly or indirectly phosphorylates P53 through check point kinase 2 (CHK2), which inhibits P53 from binding to MDM2 and being degraded by proteasomes [1, 37]. Hitherto described P53 dysfunctions include: Type A, characterized by high basal level of P53 and damaged induction of P21 after ionizing radiation (IR); Type B, characterized by low basal level of P53 and P21 and both incompetent at IR inducible up-regulation, is closely interrelated to ATM gene mutations; Type C, with normal P53 response but inability in P21 accumulation after IR, is newly detected and linked to SNPs in P21 gene [8, 37, 39]. Among them, type A is closely associated with *TP53* mutations and chemoresistance.

13q

Deletion of 13q14 is the most frequent aberration in CLL. Coded by 13q14, miR-15a (GenBank 406948)/miR-16-1 (GenBank 406950) play a well-demonstrated pathogenetic role [1, 40-42]. In CLL, *TP53* is directly regulated by miR-15a/miR-16-1 negatively and transactivates miR-15a/miR-16-1 transcription in turn [4]. This regulatory loop is similar to miR-34a to some extent which may be explained by the homology of 13q and 11q CLL-associated regions [43]. Besides, transcription-independent regulation of miR-16-1 by P53 was newly revealed HCT116 cells [23]: P53 could enhance processing from pri-microRNAs to pre-microRNAs and finally elevate level of mature miR-16-1. Besides, this *TP53*-microRNA loop may regulates downstream pathways including BCL2 family [44]: miR-15a/miR-16-1 decrease the level of antiapoptotic BCL2 and myeloid cell leukemia sequence 1 (BCL2-related) (MCL1) [4, 26, 45] while the function of Bax (coded by chromosome 13) is shifted by *TP53* [4]. In $13q^-$ CLL cases there seems a balance between increased antiapoptotic proteins and *TP53*

overexpression, which could explain the indolent course.

Trisomy 12

Trisomy 12 is common in CLL. MDM2 mapped on chromosome 12 directly inhibits P53 in MDM2-P53 autoregulatory feedback loop. It is generally overexpressed and has a different expression profile in CLL [46, 47]. Dosage effect may contribute to elevated MDM2 level in trisomy 12 cases [1]. The promising non-genotoxic MDM2 antagonist nutlin-3 induces p53-dependent apoptosis by targeting at MDM2-P53 binding, stabilizing P53 and activating P53 cascade [48]. The central role of P53 status is emphasized in sensitivity to nutlin-3 [49, 50]. It is even sufficient regardless of ATM status [51] and provides a novel therapeutic strategy for CLL including ATM-mediated chemoresistant ones. Besides, whether MDM2 polymorphism could be identified as a risk factor has been controversial [52, 53]. A very recent meta-analysis based on 7259 subjects suggests promoter SNP309G as a low-penetrant risk factor for CLL among Asians but not Caucasians [54]. However, the possible links between MDM2 polymorphism and p53 and its inner speech is still unclear.

IGHV

IGHV mutational status is accepted as one of the most reliable prognostic factors in CLL. It is associated with 11q deletion strongly [55], whereas the association for *TP53* mutation is variably discordant in different studies. Some studies prove that high-risk *TP53* alterations are strongly associated with unmutated *IGHV* status and advanced stages [1, 7, 9] while others support the opinion that the links are weak [56]. However, more and more clues suggest a mutually complementary regulation: some certain subgroups with mutated-*IGHV* have poor clinical processes, in which *TP53* polymorphism seems to be the additional modifier [57], while a subset of CLL patients with *TP53* abnormality characterized by mutated *IGHV* have stable disease [58]. The association between *IGHV* status and *TP53* mutation in aggregate is still unclear but assessment of *TP53* mutation status in patients with mutated *IGHV* may influence the choice of subsequent therapy, and vice versa.

Preview

Studies on *TP53* have revealed a complex network in the pathogenesis of CLL. *TP53* builds a story including common cytogenics and relative microRNAs. Its critical prognostic value has attracted much attention but more details are still ambiguous. Meanwhile novel agents independent of *TP53* mutational status need to be explored to further improve the prognosis.

Acknowledgement

This study was partly supported by: National Natural Science Foundation (No. 81270598), Natural Science Foundations of Shandong Province (No. Y2007C053, No. 2009ZRB14176 and No. ZR2012HZ003), Technology Development Projects of Shandong Province (No. 2007GG10, and No. 2010GSF10250), Program of Shandong Medical Leading Talent, and Taishan Scholar Foundation of Shandong Province.

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Address correspondence to: Dr. Xin Wang, Department of Hematology, Provincial Hospital affiliated to Shandong University, No. 324, Jingwu Road, Jinan, Shandong, 250021, China. Phone: 86-531-85186358 (B); 86-13156012606 (M); Fax: 0086-0531-87068707 (B); E-mail: xinwang55@yahoo.com.cn

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