

*Review*

# Malignant Lymphoma and Tumor Suppressor Genes

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Various types of tumor suppressor genes (TSG) have been reported to be mutated in malignant lymphoma. Point mutation and deletion are the major mechanisms that inactivate TSG. Alterations of the p53 gene have been analyzed well in lymphoid malignancies, and point mutations have been proved to have an important role in the progression or aggressiveness of B cell lymphoma. Recently, the silencing of gene expression by DNA hypermethylation was proposed as an alternative mechanism in inactivation of TSG. The p73, p15INK4B, and p16INK4A genes are targets of such epigenetic alterations. The ATM, PTEN, and SNF5/INI1 genes are also reported to be mutated in T and/or B cell malignancies. Recurrent chromosomal deletion may indicate the loss of candidate TSGs in the deleted interval. Cytogenetic and molecular analyses have revealed frequent and recurrent hemizygous chromosomal deletions at 6p, 6q, and 13p in malignant lymphoma. These deleted intervals have been intensively investigated to identify the candidate TSG that imply the pathogenesis of malignant lymphoma. As mentioned above, many TSG are mutated in malignant lymphoma, and these alterations could be critical in the development and progression of lymphoma. Comprehensive study of TSG is essential to understand the biological characteristics of malignant lymphoma.

**Key words** malignant lymphoma, tumor suppressor gene, chromosomal deletion

## INTRODUCTION

Human neoplasms have been shown to progress through multi-step processes of genetic alteration. The deregulation of oncogenes is one of the major steps. Chromosome translocations are major genetic alterations in hematological malignancies<sup>1,2</sup>. Oncogenes usually lie close to chromosomal breakpoints and become deregulated or mutated. Several genetic loci, such as Cyclin D1<sup>3,4</sup>, BCL2<sup>5</sup>, BCL6<sup>6,7</sup>, BCL10<sup>8</sup>, ALK<sup>9</sup>, and MALT1<sup>10,11</sup>, are sometimes disrupted by specific

chromosomal translocations in malignant lymphoma. They have been cloned near chromosomal breakpoints, and are now regarded as oncogenes with important roles in lymphomagenesis.

Another important genetic event beyond the activation of oncogenes is alteration of tumor suppressor genes (TSG). Knudson proposed the "2 hits" theory to explain the mechanism for neoplasm development through the genetic alterations of TSG based on epidemiological observation of retinoblastoma cases<sup>12</sup>. Patients with hereditary cancer syndrome have the mutated TSG in a heterozygous germ line creating the endogenous first hit, and disruption of another copy of the TSG as the second hit will develop malignancy within the target organ. This hypothesis has been confirmed by molecular biological analyses of cases of retinoblastoma<sup>13</sup>, Wilms tumor<sup>14</sup>, Li-Fraumeni syndrome<sup>15,16</sup> and familial polyposis of the colon<sup>17</sup>. In sporadic cases, two-hit inactivation of the TSG at both alleles should be necessary to induce malig-

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Received : Feb 7, 2001

Revised : Feb 4, 2002

Accepted : Feb 6, 2002

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nancies of the target organ.

Inactivation of TSG has also been reported in sporadic lymphoid malignancies. Mutations of p53<sup>18,19</sup> and p16INK4A<sup>20</sup> genes were found in some patients with lymphoid malignancies. p53 mutations have been demonstrated to be a significant prognostic factor<sup>21</sup>. In other words, alterations of TSG will directly affect the clinical features of lymphoid malignancies. Many other documented and putative TSG have been reported to be mutated in lymphoid malignancies. Many deleted chromosomal regions have been identified from karyotype analysis of lymphoma. Such frequently deleted regions might be candidates for one of the two hits of Knudson's theory. They are thought to include candidate tumor suppressor loci, which may harbor TSG. Much effort has been made in many laboratories to clone TSG from such regions.

The importance of TSG in the pathogenesis of lymphoma and the present status of the progress in cloning TSG are presented in this review.

## Inactivation of TSG

### 1. Point mutation

TSG usually have been cloned as genes responsible for familial cancer syndromes. The presence of point mutations in a germ line is strong evidence of responsibility for such syndromes. Somatic mutation in sporadic tumors is also the most common mechanism for TSG inactivation. Almost all TSG and putative TSG have point mutations or small deletions in their coding regions, and these mutations usually result in amino acid substitutions and protein truncations. Some TSG have hot spots for point mutations in the biologically important region of the respective gene<sup>22</sup>. Some mutations abrogate or change the physiological function of the genes. These changes are classified as "loss of function" or "gain of aberrant function" mutations. One of the genes best known to undergo frequent point mutations is p53. Databases for p53 mutations have been constructed in various kinds of tumors<sup>23</sup>. DNA chips, which can detect p53 mutations, are designed to exploit these data.

### 2. Chromosomal deletion

Hemizygous and homozygous chromosomal

deletion is another genetic change of TSG. Hemizygous deletions, which can be detected by loss of heterozygosity (LOH) studies using polymorphic markers, are frequently found around RB, p53, WT1, p16INK4A, and p15INK4B gene loci, demonstrating one allelic inactivation of these genes. Homozygous deletions have been found in the 9p21 region, which contains the locus of p16INK4A and p15INK4B, and is an example of the biallelic inactivation of these genes<sup>20,24</sup>. Some candidate TSG have been cloned from regions that are homozygously deleted in sporadic malignancies<sup>25-27</sup>. These regions, which show chromosomal deletions, may indicate the presence of possible TSG.

### 3. Hypermethylation of CpG islands

CpG islands (a GC-rich section of the genome usually found in the 5' region of genes) of transcriptionally-expressed genes remain unmethylated. Hypermethylation of the normally unmethylated CpG islands in the promoter regions of TSG is correlated with the loss of transcription, suggesting an alternative mechanism leading to TSG inactivation<sup>28-31</sup>.

## Tumor suppressor genes and candidates

### 1. p53 and p73

To maintain genomic stability, cells have a specific surveillance and repair system. p53, the central player in this system, is activated by the Ataxia-telangiectasia mutated (ATM) gene product in response to DNA damage<sup>32</sup>. Activated p53 can induce the cyclin-dependent kinase inhibitor, p21 (WAF1), to stop the cell cycle and allow time for the repair of damaged DNA<sup>33,34</sup>, or can induce apoptosis to remove cells with excessive genomic damage<sup>35</sup>. Recently, several genes whose transcription is induced by p53 have been cloned, including AIP1<sup>36</sup> and p53R2<sup>37</sup>. Molecular analysis of genes regulated by p53 is an effective method to reveal the multi-functional profile of p53. Through these functions p53 keeps the genome stable and suppresses the development of malignancy.

The genetic alteration of p53 in lymphoid malignancies has been reported by many investigators<sup>18,19</sup>. The incidence of mutations of the p53 gene in B cell lymphoma has been reported to

range from 10% to 40%. Approximately 20% of aggressive B cell lymphomas, excluding lymphoblastic lymphoma and small non-cleaved cell lymphoma, show p53 mutations<sup>18,21</sup>. A higher rate of p53 mutations was found in small non-cleaved cell lymphoma: 23 out of 59 (39%) patients<sup>38</sup>. On the other hand, low grade lymphoma showed about a 10% incidence of mutation of the p53 gene, but mutations of p53 are associated with histologic transformation in approximately 25–30% of follicular lymphoma<sup>39</sup>. These reports suggest that p53 mutations might have an important role in tumor progression or aggressiveness. In fact, a poor prognosis was

correlated with p53 mutation in various kinds of human malignancies<sup>40,41</sup>.

In aggressive non-Hodgkin's lymphoma (NHL) we reported that overall survival was significantly lower in patients with p53 mutations than in those with wild-type p53 (5-year survival rate: 16% versus 64%) (Fig. 1), and that p53 mutation is an important marker affecting patients' survival, independent of well-known clinical markers in the international prognostic index (IPI)<sup>21,42</sup>. Interestingly, p53 mutation had no significant effect on the survival of patients in high and high-intermediate IPI risk groups, although this mutation was significantly associated with poor survival in low and low-intermediate risk patients (Fig 1). This finding suggested: 1) the unique prognostic significance of p53 mutation in a lower risk population and 2) the presence of factors other than p53 mutation that determine prognosis in high and high-intermediate IPI risk patients.

Recently, the **p73** gene located on chromosome 1p36 was cloned and joined the p53 family<sup>43</sup>. The function of the p73 gene resembles that of p53, in terms of inducing p21 (WAF1) expression and resulting in G1 arrest and induction of apoptosis. Because of its chromosomal location, p73 was once thought to be a candidate TSG for neuroblastoma, but a recent study suggested less involvement in the development of neuroblastoma<sup>44</sup>. Kawano, et al. found no genetic changes in the p73 gene in lymphoid malignancies, but loss of mRNA expression and hypermethylation of the CpG island of the 5', untranslated region, of the p73 gene were observed in acute lymphocytic leukemia (ALL) /B-NHL cell lines as well as in primary lymphoid tumors<sup>45</sup>. These data linked epigenetic changes in the p73 gene to development and/or progression of lymphoid neoplasms.

## 2. ATM and DNA repair genes

Ataxia telangiectasia (AT), an autosomal recessive disorder characterized by cerebellar degeneration, immunodeficiency, oculocutaneous telangiectasia, genome instability, cancer predisposition and radiation hypersensitivity, is caused by mutations of a gene named **ATM**. It encodes a 350 kDa serine-threonine kinase and is located at 11q22–23<sup>46,47</sup>. ATM recognizes DNA-double strand breakage after ionizing radiation and activated ATM can phosphorylate the check-

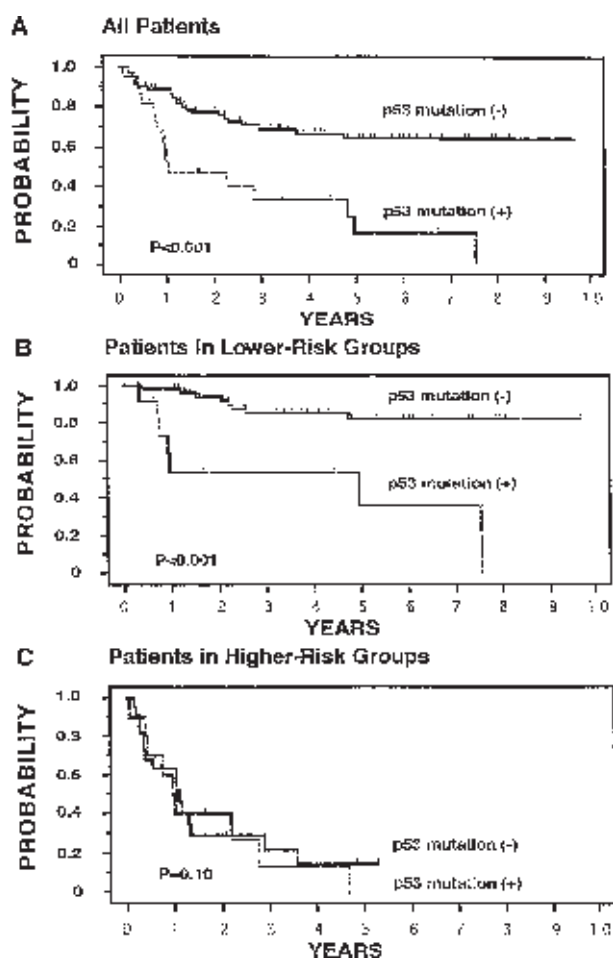


Fig. 1. Survival of patients with and without p53 mutations.

Survival with p53 mutations was significantly shorter than without p53 mutation in patients of all populations (A) and of groups at low and low-intermediate risk (B). The presence of p53 mutations did not significantly affect the survival of patients in groups at high and high-intermediate risk (C).

point kinase Chk2. The phosphorylated Chk2 can then phosphorylate p53. Using this cascade, DNA damage will result in cell-cycle arrest at the G1 stage<sup>32-34</sup>. AT patients show a marked predisposition to develop T and B cell lineage malignancies.

T-prolymphocytic leukemia (T-PLL) has been analyzed for mutations of the ATM gene. The majority of sporadic T-PLL are reported to have a hemizygous chromosomal deletion at 11q22-23, which contains the ATM gene, and showed missense mutations in the ATM gene on the remaining allele<sup>48</sup>. These reports demonstrated that somatic inactivation of ATM was involved in the pathogenesis of sporadic T-PLL and that ATM acted as a TSG in sporadic tumors of non-AT cases. Recently, biallelic mutations of the ATM gene were reported in 7 out of 12 mantle cell lymphomas<sup>49</sup>. Alteration of the ATM gene was proved to be involved in both B cell and T cell lineage malignancies.

The **NBS1** gene product is a component of the complex of DNA double strand breakage repair machinery and is located at chromosome 8q21. Patients suffering from Nijmegen syndrome, a cancer-predisposing disorder, have germ line point mutations in the NBS1 gene<sup>50</sup>. Our preliminary study identified somatic missense mutation of the NBS1 gene in some malignant lymphoma patients (unpublished data). A breakdown in the DNA repair system might have a role in the pathogenesis of malignant lymphoma.

### 3. *p15 and p16, INK4 family*

Chromosome 9p21 is a frequent site of deletions and rearrangements in many tumors, including leukemia, implying the existence of a TSG within this region<sup>51,52</sup>. The type-1 interferon gene clusters were mapped to this region, and were originally suggested as the target for the deletion in leukemia. Later studies, however, revealed that **p16INK4A**, one of the cyclin dependent kinase (CDK) inhibitors for CDK4 and CDK6<sup>53</sup>, was located in this region and possessed the basic genetic characteristics of TSG<sup>54,55</sup>.

The activity of CDK, which regulates the cell cycle progression of eukaryotic cells, is modulated by complex mechanisms including the expression of cyclins and CDK inhibitors and the phosphorylation of CDK. CDK inhibitors are thought to be negative regulators of the cell cycle, so the

disruption of these genes will result in uncontrolled cell cycle progression and cell proliferation. **p15INK4B**, which shows a high homology to p16INK4A, is located in the same region<sup>54</sup>, and may act as an effector of transforming growth factor- $\beta$  mediated cell cycle arrest<sup>56</sup>.

High-frequency homozygous deletions involving the p16/p15 locus were reported in ALL, especially in leukemia of T cell lineage (about half of cases)<sup>24,57</sup>. Such deletions and somatic mutations of p16INK4A are not so frequent in B cell lymphoma<sup>20,58,59</sup>. Some investigators have found genetic alterations of p16INK4A in adult T cell leukemia/lymphoma (ATLL) at relatively high frequency<sup>60</sup>. The homozygous deletions in the p16/p15 locus seem to be associated with the progression toward high-grade tumor<sup>61,62</sup>.

Hypermethylation of the INK4 family has also been studied in various types of tumors, including hematological malignancies. Selective inactivation by hypermethylation of either p16INK4A or p15INK4B has been observed in hematological malignancies according to the respective tumor type<sup>31,63-66</sup>. Methylation of p15INK4B, for example, occurs frequently in acute myeloid leukemia (AML), ALL and myelodysplastic syndrome (MDS), but methylation of p16INK4A in AML, ALL and MDS appears to be rare. Both methylation of p16INK4A and p15INK4B in multiple myeloma was found with a high frequency. In contrast, neither p16INK4A nor p15INK4B are methylated at any stage of chronic myelogenous leukemia (CML).

In malignant lymphoma, both p16INK4A and p15INK4B have been reported to be frequently methylated<sup>67</sup>. The reported methylation of p15INK4B and p16INK4A genes was 64% and 32% of B cell lymphomas, and 44% and 22% of T cell lymphomas, respectively. Because high-grade B cell lymphoma showed more frequent methylation of p15INK4B and p16INK4A (78% and 50%, respectively) than low grade B cell lymphomas (55% and 21%, respectively), the p15 and p16 gene silencing by methylation is suggested to be associated with aggressiveness of lymphoma.

The INK4A locus gives rise to a transcript called **p14/19ARF** gene that is separate from p16INK4A and transcribed from another exon using a different reading frame<sup>68</sup>. p14/19ARF can

arrest the cell cycle in a p53-dependent manner. p14/19ARF binds to MDM2 and promotes the rapid degradation of MDM2<sup>69</sup>. p14/19ARF-promoted MDM2 degradation is associated with MDM2 modification and concurrent p53 stabilization and accumulation.

The functional consequence of p14/19ARF-regulated p53 levels via MDM2 proteolysis is evidenced by the ability of ectopically-expressed p14/19ARF to restore a p53-imposed G1 cell cycle arrest that is otherwise abrogated by MDM2. These functional aspects of p14/19ARF may explain the route of unregulated cell proliferation and tumor development when it is inactivated. In primary tumors and cell lines, the majority of biallelic deletions of p16INK4A extend to include the first exon of p14/19ARF, but most intragenic p16INK4A mutations do not disrupt p14/19ARF function<sup>70</sup>. Taniguchi, et al. reported that the lack of expression of p14/19ARF was found in diffuse, large B-cell lymphoma (DLBCL). Nevertheless, follicular lymphoma, myeloma and AML expressed p14/19ARF, and p16INK4A; p14/19ARF expression seemed to be affected differently among these malignancies<sup>71</sup>. These observations suggest that further studies of the INK4A locus and p14/19ARF will be required to determine the role of these factors in tumor progression.

#### 4. *PTEN*

The **PTEN/MMAC1** gene located at 10q23.3 encodes a protein and is a novel TSG candidate with a domain homologous to protein phosphatases as well as a domain homologous to tensin, a cytoskeletal protein<sup>25,72</sup>. Phosphatase has been thought to be a potential TSG<sup>73</sup>. In contrast, some protein kinases have been identified as oncogenes<sup>74</sup>. The PTEN/MMAC1 gene is the first phosphatase to be identified as a TSG candidate, and mutations have been found frequently in various kinds of malignant tumors. Germ line mutations have been identified in Cowden disease patients, an autosomal dominant disorder associated with an increased risk of developing both benign and malignant tumors.

Various kinds of primary sporadic tumors show mutations in PTEN/MMAC1, including glioblastoma<sup>75</sup>, endometrial carcinoma<sup>76</sup>, and prostate cancer<sup>77</sup>. We examined 29 cases of primary NHL for mutations in the PTEN/

MMAC1 gene. One case of DLBCL had an 11 bp deletion, which contained the first ATG<sup>78</sup>. Missense mutations and homozygous deletions have also been reported in a small percentage of lymphoma cases<sup>79</sup>. These data indicate that alterations of the PTEN/MMAC1 gene are also involved in the pathogenesis of some NHL.

#### 5. *SNF5/INI1*

The chromosomal deletions of 22p11, the region of the **SNF5/INI1** gene locus, were frequently observed in lymphoid malignancy<sup>80</sup>. SNF5/INI1 has critical roles in chromatin remodeling, and is thought to be a candidate TSG, because germ line mutations of this gene have been reported in rhabdoid tumors of children<sup>81</sup>. We performed mutation analysis of this gene in primary lymphoid malignancies as well as in hematopoietic cell lines, and identified missense and nonsense mutations in one primary tumor and two cell lines<sup>82</sup>. The frequency of these genetic alterations was relatively low, but alteration of this gene in lymphoma has been suggested to have a role in the genesis of lymphoma.

#### Chromosomal deletions, candidate regions for new TSG

Karyotype analysis and other experiments have pointed to many chromosomal deletions in sporadic NHL, and some of them are reproducible. A complete understanding of the pathogenesis of NHL may require learning the clinical and biological meaning of such deletions. Recurrent chromosomal deletion may indicate the presence of candidate TSG in the deleted interval. So far, using the reverse-genetic approach, some candidate TSG have been cloned from chromosomal regions recurrently deleted in sporadic tumors<sup>25,26,27</sup>. The chromosomal deleted regions analyzed intensively in lymphoid malignancies are described below (Fig. 2).

##### 1. *6p*

LOH mapping is a method used widely for characterizing solid tumors, in which karyotyping is not practical, to identify genetic changes. In hematological malignancies it is easier to obtain sufficient information on chromosomal

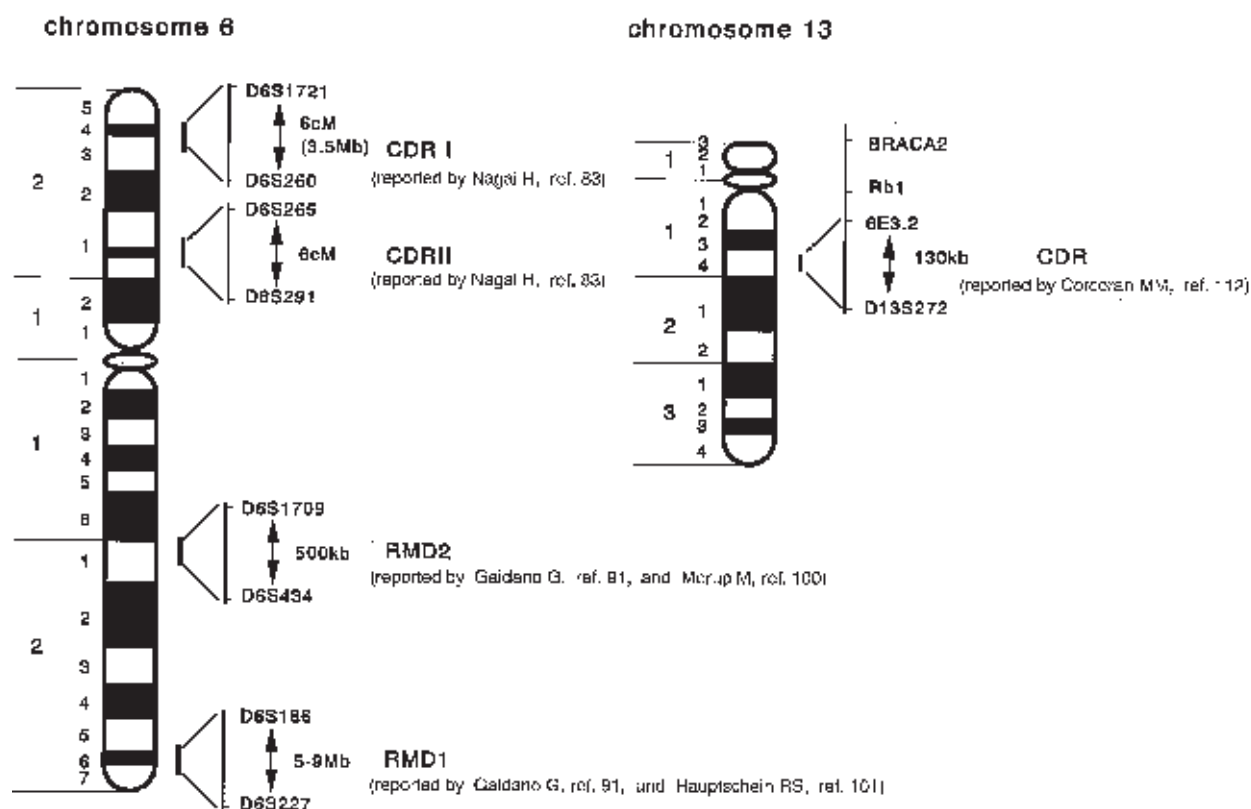


Fig. 2. Molecular delineation of chromosomal-deleted regions at chromosome 6 and 13. CDR: common deleted region, RMD: region of minimal molecular deletion, cM: centimorgan, Mb: megabase

alterations by karyotyping, so allelotyping studies rarely have been performed. Because of the presence of cryptic chromosomal deletions through karyotyping, allelotyping studies could be another powerful method to evaluate genetic deletions. By a comprehensive allelotyping study using 39 highly-informative microsatellite markers distributed among all autosomal chromosomes, we found frequent LOH at 6p in B-cell NHL<sup>83</sup>. The most frequent LOH occurred at polymorphic microsatellite marker D6S1721, where 9 of 18 of the informative cases (50%) had allelic losses. Other regions with frequent LOH (> 25%) were 1q, 3p, and 6q, respectively.

To identify the common deleted regions (CDR) of 6p, we performed fine deletion mapping using 26 highly-polymorphic microsatellite markers on 6p. LOH patterns indicated two CDR on 6p: one between D6S1721 and D6S260 (at 6p23-24), and the other between D6S265 and D6S291 (at 6p21). The genetic distance of both CDR was 6 cM. p21 (WAF1), which inhibits almost every kind of CDK, is located between D6S276 and D6S439 at 6p21.2. This interval was included in

the CDR at 6p21. Thus, mutations of p21 (WAF1) were screened in NHL cases, yet no point mutations, other than polymorphisms, could be found in this gene.

Frequent allelic loss at 6p also has been reported in other tumors by allelotyping, such as renal cell carcinoma<sup>84</sup>, cervical carcinoma<sup>85,86</sup>, and esophageal squamous cell carcinoma<sup>87</sup>. The data suggest that these two loci might harbor novel putative TSG responsible for the genesis of various tumors. Recently, we have cloned the CDR at 6p23-24 by yeast artificial chromosome (YAC) clones. The physical distance of this interval was approximated at 3.5 Mb by this physical mapping<sup>83</sup>.

## 2. 6q

Karyotypic abnormalities of chromosome 6q represent one of the most frequent cytogenetic alterations observed in B-cell NHL<sup>2,88</sup>. Cytogenetic analysis using 459 specimens of NHL showed at least 3 loci that are commonly deleted on chromosome 6q<sup>89</sup>. These regions were termed

regions of minimal cytogenetic deletion (RCD), with RCD1 located at 6q25-q27, RCD2 at 6q21, and RCD3 at 6q23, respectively. The chromosomal deleted region at 6q11-q21 was also delineated using micro-FISH analysis<sup>90</sup>. One hundred twenty-six, out of 459, NHL cases (27.5%) had structural abnormalities of chromosome 6, and 94 (20.5%) were chromosomal deletions.

Using a molecular biological technique, chromosome 6q was also proven to have 2 distinct regions of minimal molecular deletions (RMD) at 6q25-q27 (RMD1) and 6q21-q23 (RMD2), respectively<sup>91</sup>. RCD1 and 2, cited above, corresponded mostly to RMD1 and RMD2, respectively. The chromosomal deletions at 6q, especially in its distal region, were reported in various kinds of solid tumors, for example ovarian cancer<sup>92,93</sup>, hepatoma<sup>94</sup>, breast cancer<sup>95,96</sup>, and colon cancer<sup>97</sup>.

Chromosome-mediated transfer experiments in some tumor cell lines demonstrated that normal chromosome 6 could suppress their transformed phenotype<sup>98,99</sup>. Thus, the long arm of chromosome 6 has been thought to harbor a putative TSG. Fine-deletion mapping of the commonly deleted regions of 6q21, using lymphoblastic leukemia and NHL samples, narrowed RMD2 to an interval of less than 500 kb between D6S1709 and D6S434<sup>100</sup>. Moreover, a physical mapping project on 6q26-27 confirmed that B-cell RMD1 is located between D6S186 and D6S227. Its size was estimated as 5-9 Mb<sup>101</sup>.

The megabase sequencing project and other efforts are now concentrated on these regions, but no good candidate TSG have been cloned to date. AF6<sup>102</sup>, located in RMD1, was also disrupted in some hematological malignancies by chromosomal translocation. And BACH2<sup>103</sup>, located on 6q15, could reduce tumorigenic activity of some lymphoid cell lines. However, no somatic mutations in the coding region of these two genes have been found in NHL.

### 3. 13q

Cytogenetic analysis has shown that recurrent abnormalities of chromosome 13q14, including translocations and deletions, are the most common structural change in B-cell chronic lymphocytic leukemia (CLL)<sup>104,105</sup>. This chromosomal deletion is the common genetic alteration in CLL. Molecular analysis also

revealed 13q deletion in cases without karyotypic changes<sup>106</sup>. This region is very close to the RB1 locus, but the frequently deleted region was found around D13S25, telomeric to the RB1 locus<sup>107-109</sup>. This region was also reported to be deleted in B-cell NHL with a relatively high incidence (25-50%)<sup>110,111</sup>.

The microsatellite marker showing the most frequent deletion at 13q14 is D13S319<sup>110,112</sup>. It is located about 1 Mb telomeric to the RB1 locus. This deleted region is actually a recurrent genetic alteration, and is thought to be a strong candidate locus for TSG. Nevertheless, inactivation of the RB1 gene seems to play a role in the malignant transformation of some lymphoid malignancies<sup>113</sup>. The deletion at 13q14 was analyzed for its possible correlation with the clinicopathological features of NHL. This deletion represents an early chromosomal change and shows a preferential association with mantle cell lymphoma<sup>114</sup>. Several genes located on 13q14 were cloned as candidate TSG<sup>115</sup>, but these genes have not been confirmed as real TSG for lymphoid malignancies. A recent physical mapping project<sup>112</sup> narrowed the common deleted region adjacent to D13S319 into a 130 kb interval. This interval is very small and thought to have been sequenced already. The candidate TSG, which is involved in pathogenesis of lymphoid malignancy, is expected to be cloned soon.

Another somatic deletion in CLL has been reported on chromosome 13q12.3 encompassing BRCA2, which is centromeric to the RB1 gene<sup>116</sup>. However, BRCA2 might not be a candidate TSG for lymphoid malignancies, and there is a possibility of another TSG in this region.

As mentioned above, TSG other than oncogenes could have important roles in the development and progression of lymphoma. Comprehensive studies of TSG are crucial to understand the biological characteristics of malignant lymphoma. Some evidence has suggested that impairment of TSG, which affects the cellular response to DNA damage, might enhance susceptibility to chromosomal translocations<sup>117</sup>. Generally, specific chromosomal translocations are thought to represent early hits on genetic material, and will determine the subtype of lymphoid malignancies. Alterations of TSG, a later event, will affect tumor progression. It is very important to identify poor risk patients to improve the

outcome of treatment for malignant lymphoma. A complete database of TSG alterations in lymphoma and a full understanding of the clinical features of each tumor subtype are indispensable to improving the management of malignant lymphoma and the development of new strategies for treatment.

Genome sequencing will be completed early in this century: and almost all genes will be cloned and their precise chromosomal location will be determined. At this stage there is an urgent need to provide researchers with all possible information on the locations of unique chromosomal alterations, especially deletions, to identify the tumor suppressor genes. Cloning a disease-responsible gene using molecular and cytogenetic techniques will open the door to post-genome medicine.

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