Deletions in the Long Arm of Chromosome 10 in Lymphomas With t(14;18): A Pathogenetic Role of the Tumor Suppressor Genes PTEN/MMAC1 and MXII?

To the Editor:

The translocation t(14;18)(q32;q21), characteristic for follicular lymphomas and a subset of diffuse large cell lymphomas, juxtaposes the bcl-2 proto-oncogene with the Ig heavy-chain (IgH) gene. This results in deregulation of the bcl-2 gene expression and elevation of BCL-2 protein, which protects the cells against induction of programmed cell death and, thus, confers a survival advantage leading to immortalization of t(14;18)-carrying cells. The acquisition of additional chromosomal aberrations is necessary for the malignant transformation and clonal progression of BCL-2 overexpressing lymphocytes. These secondary changes can be observed by karyotyping in more than 90% of lymphomas with t(14;18).1,2

By karyotyping a series of 201 lymphomas at the Department of Human Genetics in Kiel, we detected deletions in the long arm of chromosome 10 in 6 of 57 (11%) B-cell lymphomas with a t(14;18), but in only 1 of 144 (1%) lymphomas without a t(14;18). Thus, loss in 10q seems to be a characteristic secondary abnormality for t(14;18)-positive lymphomas (P < .001). The frequency of del(10q) in t(14;18)-positive lymphomas observed in our series is in line with other cytogenetic studies reporting abnormalities of the long arm of chromosome 10 in 7 of 66 (11%) and 9 of 75 (12%) follicular lymphomas.3

The common region of cytogenetic loss in our series encompassed the chromosome band 10q24, suggesting the existence of a tumor suppressor gene involved in the pathogenesis of t(14;18)-positive lymphomas in this region. So far, two tumor suppressor genes have been identified within this region, namely PTEN/MMAC1 in 10q23.34-6 and lymphomas in this region. So far, two tumor suppressor genes have been suppressor gene involved in the pathogenesis of t(14;18)-positive lymphoma tissue was available for six patients shown to contain loss of one PTEN/MMAC1 allele by FISH. Additionally, a further t(14;18)-positive primary lymphoma not evaluable by FISH but containing a karyotypically detectable deletion in 10q and the cell line Karpas 422 were included. Except for well-known polymorphisms, no alterations of the PTEN/MMAC1 gene were detected in any of the primary lymphomas. Nevertheless, the cell line Karpas 422 was found to contain a splice acceptor site mutation (A → C) at position −2 of exon 3 of the PTEN/MMAC1 gene (Fig 1B), which was confirmed by sequencing a second subclone of this cell line. Remarkably, the same mutation has been recently described in a primary glioblastoma.10 To determine the pathogenetic relevance of this alteration, reverse transcriptase-polymerase chain reaction (RT-PCR) analysis was performed on Karpas 422 with primers surrounding exon 3.11 This failed to amplify the expected germline 397-bp fragment but showed a shorter PCR product, which, by sequencing, was shown to be a splice variant caused by skipping of the 45-bp sized exon 3 (Fig 1C). Thus, the intact PTEN/MMAC1 transcript is completely absent in Karpas 422 due to deletion of the first and mutation of the second allele. The truncated transcript lacks part of conserved protein domain with high homology to tensin and auxillin and thus can be assumed to lack activity.12

In summary, our data provide evidence that deletions in the long arm of chromosome 10 are recurrent secondary changes in t(14;18) lymphomas. As to our FISH analyses, the distal border of the interstitial deletions in most cases is proximal to the MXII gene, rendering this gene as well as the candidate gene DMBT1, which is localized more distally in 10q25.3-26.13 highly unlikely as tumor suppressors in germinal center lymphomas. We detected consistent loss of the PTEN/MMAC1 gene by FISH in the cases investigated. Nevertheless, a mutation leading to inactivation of the second allele has been detected only in the cell line Karpas 422 but not in primary lymphomas. Inactivating mutations have also been described in a series of other cell lines derived from hematological neoplasms.12,14,15 In accordance with our results, alterations of the PTEN/MMAC1 have been reported by two groups to occur only in a small minority of unselected primary lymphoid malignancies. Grønbæk et al14 reported mutations of the PTEN/MMAC1 in 2 of 170 and Sakai et al15 in 1 of 42 primary lymphoid malignancies. Considering the scarcity of PTEN/MMAC1 mutations in primary lymphoid malignancies, the existence of a thus far unknown tumor suppressor gene in 10q involved in the pathogenesis of at least germinal center lymphomas might be assumed.

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