Mucosa-Associated Lymphoid Tissue Lymphoma: Novel Translocations Including Rearrangements of ODZ2, JMJD2C, and CNN3

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Abstract

Purpose: The well-known translocations identified in MALT lymphomas include t(11;18)/API2-MALT1, t(1;14)/IGH-BCL10, and t(14;18)/IGH-MALT1. Molecular investigations have suggested that these three disparate translocations affect a common pathway, resulting in the constitutive activation of nuclear factor-κB. However, the vast majority of MALT lymphomas are negative for any of the above-mentioned translocations and the underlying pathogenesis is unclear.

Experimental Design: Fresh tissue of 29 gastric and extragastic MALT lymphomas was studied for genetic aberrations by conventional karyotyping, long-distance inverse PCR (LDI-PCR), fluorescence in situ hybridization (FISH), reverse transcription-PCR (RT-PCR), and real-time quantitative RT-PCR (QRT-PCR).

Results: Conventional cytogenetics, FISH, and RT-PCR identified aberrations in 26 of 29 MALT lymphoma. Balanced translocations were found in 21 cases. IGH was rearranged in the majority of cases with balanced translocations (n = 17/21); 3 cases had t(11;18)/API2-MALT1 and 1 case had novel t(6;7)(q25;q11), respectively. IGH partner genes involved MALT1, FOXP1, BCL6, and four new chromosomal regions on chromosome arms 1p, 1q, 5q, and 9p. LDI-PCR identified three novel partner genes on 1p (CNN3), 5q (ODZ2), and 9p (JMJD2C). FISH assays were established and confirmed LDI-PCR results. QRT-PCR showed deregulation of the novel genes in the translocation-positive cases.

Conclusions: Our study expands the knowledge on the genetic heterogeneity of MALT lymphomas.

B-cell non–Hodgkin lymphomas (B-NHL) are malignant clonal expansions of B cells at various stages of maturation. Chromosomal rearrangements, including translocations of immunoglobulin (IG) loci and creation of chimeric protein(s), are implicated in the pathogenesis of B-cell lymphoma. The former results in the dysregulation of oncogenes located at the partner chromosome loci (1). Some IG translocations are associated with certain subtypes of lymphoma, showing distinct pathologic, immunophenotypic, and clinical features. Examples include the involvement of MYC in Burkitt’s lymphoma and BCL1 in mantle cell lymphoma. These translocations may therefore be useful as diagnostic markers and provide important insights into the molecular mechanisms of tumor development.

Mucosa-associated lymphoid tissue (MALT) lymphoma, the third most common B-NHL, is a distinct clinicopathologic entity. The B cells of MALT lymphoma share the cytologic features and immunophenotype of marginal zone B cells. MALT lymphoma has some unique features in comparison with other types of B-cell lymphomas and exemplifies the close relationship between chronic inflammation and lymphomagenesis. A strong association has been found between chronic infection with Helicobacter pylori and gastric MALT lymphoma (2). As opposed to their gastric counterpart, extragastic MALT lymphomas are thought to arise predominantly in patients with autoimmune diseases (3). Another clinical peculiarity of MALT lymphoma is the distinct tendency of intraorgan and interorgan dissemination (4). This characteristic might reflect a special homing pattern of lymphocytes generated within a MALT environment, which has been shown to differ between gastrointestinal and nongastrointestinal MALT (5).

The understanding of the biology of MALT lymphoma has significantly improved in recent years, in part through the application of standard cytogenetic analyses. The common translocations identified in MALT lymphomas include t(11;18)/API2-MALT1, t(1;14)/IGH-BCL10, and t(14;18)/IGH-MALT1. Molecular investigations have suggested that these three disparate translocations seem to affect a common
pathway, resulting in the constitutive activation of nuclear factor-κB (NF-κB; ref. 6). However, the vast majority of MALT lymphomas are negative for any of the above-mentioned translocations and the exact underlying pathogenesis remains unclear (7).

In this study, we investigated 29 MALT lymphomas for genetic aberrations. We report on the identification of several novel translocations in MALT lymphoma.

Materials and Methods

Clinical specimens. Twenty-nine MALT lymphoma cases with fresh tumor material available for cytogenetic analysis were studied. For inclusion in this study, the cases were required to fulfill the histologic and immunohistologic criteria defined for the respective entities in the WHO classification of tumors of hematopoietic and lymphoid tissues. The immunophenotype of the tumor cells, as assessed on paraffin sections, was CD20+, cyclin D1, CD23, CD5, Bcl-6, CD10+. Bcl-6 negativity was also found in patient 17 with IGH-BCL6 rearrangement. Biopsies or surgical resection specimens were retrieved from the files of the Department of Pathology, Medical University of Vienna, except one cutaneous MALT lymphoma case that was provided by the Department of Dermatology in Graz. Among the 29 MALT lymphoma cases, 7 involved the ocular adnexa, 7 the parotid gland (including 4 cases with regional lymph node infiltration), 2 the stomach, 6 the skin, 2 the lung, 1 the thyroid, 1 the liver, 1 the esophagus, 1 the kidney (primary localization pharynx), and 1 s.c. lesion (primary localization lacrimal gland). The presence of tumor cells (>80% infiltration) was evaluated in all cases. The localization pharynx), and 1 s.c. lesion (primary localization lacrimal gland). The presence of tumor cells (>80% infiltration) was evaluated in all cases. The localization was confirmed by CD20 +, cyclin D1 -, CD23 -, CD5 -, Bcl-6 -, CD10 -. Bcl-6 positivity was observed in 12 cases and exclusively unbalanced translocations showed a rearrangement of 14q32, 1 case the well known t(11;18), and 1 case a novel t(6;7). Among 10 the cases with 14q32 translocation, FISH confirmed IGH-MALT1 rearrangement in 4 cases, IGH-FOXp1 in 1 case, and IGH-BCL6

Translational Relevance

The majority of B-cell lymphomas have recurrent and disease-specific clonal chromosomal abnormalities. These aberrations may be useful diagnostic markers and contribute to the pathogenesis of B-cell malignancies. Paradigms are translocations of MYC in Burkitt’s lymphoma and BCL1 in mantle cell lymphoma. About extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas), attention has largely focused on the three known translocations t(11;18)/API2-MALT1, t(14;18)/IGH-MALT1, and t(1,14)/IGH-BCL10 and their relationship to the activation of the nuclear factor-κB pathway. However, genetic aberrations and the underlying pathogenesis are unclear in the majority of the cases. This article identifies several unknown genetic rearrangements that are linked to an unrecognized variety of biological functions. Our results provide new insights into the genetic heterogeneity of MALT lymphoma, suggesting a markedly diverse pathogenesis. The various novel genetic aberrations may serve as important diagnostic and prognostic markers, and the diverse pathogenesis may be relevant for the development of therapeutic strategies in MALT lymphoma.

Long-distance inverse PCR. DNA of patients 1, 4, 18, 19, 20, 22, 26, and 28 was isolated from the fresh tumor samples using a High Pure PCR Template Preparation kit (Roche). The long-distance inverse PCR (LDI-PCR) for the joining and switch regions was done as described previously (9, 10). Briefly, high molecular weight DNA was digested with restriction enzymes for 3 to 4 h at 37°C. After phenol/chloroform extraction, 0.4 μg of digested DNA was ligated at 15°C overnight with T4 DNA ligase. Restriction digests included BglII, HindIII, PsiI, and XbaI. After purification, the ligated DNA was amplified in nested PCRs. PCR products were run on agarose gels. Bands were excised from the gels and sequenced using an ABI Prism 3100 (PE Applied Biosystems). Sequences were compared with the Genbank database using BLAST program.3

Fluorescence in situ hybridization analysis. For the detection of the various MALT lymphoma-associated translocations, the following probes flanking the breakpoint regions were used: bacterial artificial chromosomes RP11-1077C10, RP11-36L4, RP11-108011, and RP11-40K4 for BCL10, RP11-215K24 and RP11-522N9 for FOXp1, RP11-465K1 and RP11-335D10 for CNN3, RP11-79K3 and RP11-77E14 for IMD2C, RP11-13H20 and RP11-14K9 for ODZ2, and commercially available probes for IGH, MALT1, and BCL6 (Vysis). The cutoff value for the diagnosis of each probe set was the mean percentage of cells with a false-positive signal constellation plus 3 SDs, as assessed on tissue from 20 reactive lymph nodes. Fluorescence in situ hybridization (FISH) procedure was done according to published standard methods (8).

RT-PCR. RNA was isolated from archival formalin-fixed, paraffin-embedded lymphoma tissues. Detection of t(11;18)/API2-MALT1 by RT-PCR was done as previously described (7).

Quantitative RT-PCR. For the evaluation of up-regulation of MALT lymphoma-associated genes, frozen tumor samples of 20 MALT lymphomas, 5 splenic marginal zone lymphoma (SMZL), 21 other B-NHLs, and 9 normal lymph nodes were used for RT-PCR as described previously (11). High RNA quality was confirmed using the Agilent Bioanalyzer 2100 (Agilent Technologies). QRT-PCR analysis was done on the ABI Prism 7000 sequence detection system (Applied Biosystems). Gene expression assays (Assay-on-Demand) for the MALT lymphoma-associated candidate genes were Hs00393060_m1, Hs00156565_m1, Hs00325678_m1, Hs00212860_m1, Hs00198984_m1, Hs00153379_m1, Hs00153380_m1, Hs00325678_m1, Hs00198984_m1, and Hs00364763_m1. Transcript levels were normalized for those of GAPDH with restriction enzymes for 3 to 4 h at 37°C. After phenol/chloroform extraction, 0.4 μg of digested DNA was ligated at 15°C overnight with T4 DNA ligase. Restriction digests included BglII, HindIII, PsiI, and XbaI. After purification, the ligated DNA was amplified in nested PCRs. PCR products were run on agarose gels. Bands were excised from the gels and sequenced using an ABI Prism 3100 (PE Applied Biosystems). Sequences were compared with the Genbank database using BLAST program.3

Results

High frequency of IGH rearrangements. To identify novel translocations in MALT lymphoma, cytogenetic analyses were done on fresh tumor samples of 29 cases. Conventional karyotyping showed aberrations in 17 of 29 cases (59%). Among the 17 aberrant karyotypes, balanced translocations were observed in 12 cases and exclusively unbalanced translocations in 5 cases (Table 1). Ten of 12 cases with balanced translocations showed a rearrangement of 14q32, 1 case the well known t(11;18), and 1 case a novel t(6;7). Among 10 the cases with 14q32 translocation, FISH confirmed IGH-MALT1 rearrangement in 4 cases, IGH-FOXp1 in 1 case, and IGH-BCL6

in 1 case; in the remaining cases, unknown IGH partners were located on 9p (n = 2), 5p (n = 1), and 1q (n = 1; Fig. 1).

About the 12 of 29 cases (41%) without clonal cytogenetic aberrations, normal metaphases may reflect proliferating non-tumor cells. We did RT-PCR for API2-MALT1 and FISH with IGH flanking probes on interphases to detect potential genetic rearrangements in tumor cells.

API2-MALT1 fusion transcripts were detected in two cases and IGH translocations in seven cases. The latter seven cases were studied with FISH probes for MALT1, BCL10, FOXP1, and BCL6. Only one case (case 19) revealed a rearrangement of MALT1. For the other six cases, the IGH partner remained unknown. In summary, we detected IGH rearrangements in 17 of 29 cases (70%).

ODZ2, JMJ2C, and CNN3 are novel IGH partner genes. To characterize the translocation breakpoints in cases with known IGH translocation (after cytogenetic and FISH analysis), eight cases with sufficient material for LDI-PCR were investigated.

Among these eight patients, cases 18, 19, 20, and 22 had t(14;18)/IGH-MALT1, case 28 had t(3;14)/IGH-FOXP1, and cases 1, 4, and 26 had unknown partner genes.

About the cases with t(14;18)/IGH-MALT1, the breakpoints were identified in cases 18 and 22 (see Supplementary Table S1);

### Table 1. Genetic aberrations in MALT lymphoma

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex/ age</th>
<th>Site</th>
<th>Cytogenetic aberrations</th>
<th>Balanced translocations (assessed by FISH, RT-PCR, and LDI-PCR)</th>
<th>Percentage of cells with split signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31/F</td>
<td>LN (parotid gland*)</td>
<td>46,XX[20]</td>
<td>t(1;14)/IGH-CN2N3</td>
<td>62% †</td>
</tr>
<tr>
<td>2</td>
<td>77/M</td>
<td>Ocular adnexa</td>
<td>46,XY[9]</td>
<td>t(5;14)/IGH-ODZ2</td>
<td>41% †</td>
</tr>
<tr>
<td>3</td>
<td>32/M</td>
<td>Skin</td>
<td>46,XY[4]</td>
<td>t(5;14)/IGH-ODZ2</td>
<td>39% †</td>
</tr>
<tr>
<td>4</td>
<td>18/F</td>
<td>Skin</td>
<td>48,XX,+18,del(6)(q21), t(5;14)[q34;q32][5]</td>
<td>t(5;14)/IGH-ODZ2</td>
<td>39% †</td>
</tr>
<tr>
<td>5</td>
<td>53/F</td>
<td>Ocular adnexa</td>
<td>46,XX,t(6;7)(q25; q11)[2]/46,XX[8]</td>
<td>ish 7q11(RP11-731K22 sep RP11-813J7x1)</td>
<td>42%</td>
</tr>
<tr>
<td>6</td>
<td>62/F</td>
<td>Ocular adnexa</td>
<td>46,XX[6]</td>
<td>t(IGH-unknown partner region)</td>
<td>48%</td>
</tr>
<tr>
<td>7</td>
<td>42/F</td>
<td>Ocular adnexa</td>
<td>46,XX[5]</td>
<td>t(IGH-unknown partner region)</td>
<td>29%</td>
</tr>
<tr>
<td>8</td>
<td>35/M</td>
<td>Parotid gland</td>
<td>46,XY[25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>88/M</td>
<td>Stomach</td>
<td>47,XY,t(1;14)(q32;q32), +12[1]/47, XY,t(1;14)(q32;q32), del(9)(q22), 12[10]/46,XY[6]</td>
<td>t(IGH-unknown partner region)</td>
<td>71%</td>
</tr>
<tr>
<td>10</td>
<td>73/F</td>
<td>Skin</td>
<td>47,XX,dup(1)[q12q23], +12[8]/46,XX,dup(1)[q12q23], der(3)[p13]/12[12];12[12], +12-13[3]/46,XX[11]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>61/F</td>
<td>Esophagus</td>
<td>49,XX,+3,+6(10), +18[12]/46,XX[13]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>68/M</td>
<td>Kidney (pharynx*)</td>
<td>48,XY,+3,+6[10],46,XY[9]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>76/M</td>
<td>Stomach</td>
<td>46,XY[4]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>52/M</td>
<td>Skin</td>
<td>46,XY[3]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>48/M</td>
<td>LN (parotid gland*)</td>
<td>46,XY[20]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>77/F</td>
<td>S.c. lesion (lacrimal gland*)</td>
<td>47,XX,+18[3]/46,XX[3]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>41/F</td>
<td>Ocular adnexa</td>
<td>48,XX,+3,+18[5]/46,XX[2]</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>49/M</td>
<td>Ocular adnexa</td>
<td>48,XY,+3,+12,13,t(14;18)[q32;q21][10]</td>
<td>t(14;18)/IGH-MALT1</td>
<td>77% †</td>
</tr>
<tr>
<td>19</td>
<td>54/M</td>
<td>Lung</td>
<td>46,XY[20]</td>
<td>t(14;18)/IGH-MALT1</td>
<td>37% †</td>
</tr>
<tr>
<td>20</td>
<td>66/M</td>
<td>LN (parotid gland*)</td>
<td>47,XY,t(12)[q10],t(14;18)[q32;q21], -17,+18,+mar,inc[2]/46,XY[28]</td>
<td>t(14;18)/IGH-MALT1</td>
<td>54% †</td>
</tr>
<tr>
<td>21</td>
<td>46/M</td>
<td>Skin †</td>
<td>46,XY,dup(1)[q12q42], del(6)[q23], dup(12)[q22q43], t(14;18)[q32;q21][8]/46,XX[7]</td>
<td>t(14;18)/IGH-MALT1</td>
<td>36% †</td>
</tr>
<tr>
<td>22</td>
<td>63/F</td>
<td>Liver †</td>
<td>50,XX,+3,+4,13,t(14;18)[q32;q21], +18[12]/51, ide, +18[2]/46,XX[16]</td>
<td>t(14;18)/IGH-MALT1</td>
<td>77% †</td>
</tr>
<tr>
<td>23</td>
<td>39/M</td>
<td>Parotid gland</td>
<td>45,XY,t(11;18)[q21;q21], -18, der(18)[p11][12], i(18)[p11][2], inc[2]/46,XY[6]</td>
<td>t(14;18)/API2-MALT1</td>
<td>—</td>
</tr>
<tr>
<td>24</td>
<td>79/M</td>
<td>Lung</td>
<td>46,XY[3]</td>
<td>t(11;18)/API2-MALT1</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>31/M</td>
<td>LN (parotid gland*)</td>
<td>46,XY[30]</td>
<td>t(11;18)/API2-MALT1</td>
<td>—</td>
</tr>
<tr>
<td>26</td>
<td>50/F</td>
<td>Parotid gland</td>
<td>47,XY,t(9;14)[p24;q32], add(2)[q36], add(11)[p15], mar, +18[2]/46,XX[2]</td>
<td>t(9;14)/IGH-JMJD2C</td>
<td>71% †</td>
</tr>
<tr>
<td>27</td>
<td>81/M</td>
<td>Ocular adnexa</td>
<td>48,XY,add(3)[p24], del(3)[p21], +7, t(9;14)[p24;q32], int[10]/46,XX[12]</td>
<td>t(9;14)/IGH-JMJD2C</td>
<td>49% †</td>
</tr>
<tr>
<td>28</td>
<td>64/M</td>
<td>Thyroid gland ‡</td>
<td>47,XY,t(3;14)[p14;q32],[11]/47,XY, t(3;14)[p14.1;q32], +22[4]/46,XY[16]</td>
<td>t(3;14)/IGH-FOX1</td>
<td>78% †</td>
</tr>
<tr>
<td>29</td>
<td>41/F</td>
<td>Skin</td>
<td>46,XX,t(3;14)[q27;32][8]/46,XX[7]</td>
<td>t(3;14)/IGH-BCL6</td>
<td>74% †</td>
</tr>
</tbody>
</table>

Abbreviation: LN, lymph node.
*Primary localization.
†Percentages of aberrant interphases correlate for IGH and partner gene probes.
‡Cases according to Streubel et al. (8).
§Case according to Streubel et al. (11).
LDI-PCR for the joining and switch regions was unsuccessful in cases 19 and 20. LDI-PCR results for the t(3;14)/IGH-FOXP1 case were published previously (see Supplementary Table S1; ref. 11). Among the t(IGH)+ cases with unknown partner genes, LDI-PCR identified CNN3 as the IGH partner on chromosome 1 (case 1), ODZ2 on chromosome 5 (case 4), and JMJD2C on chromosome 9 (case 26; see Supplementary Table S1). The localizations of the 14q32 breakpoints of the six cases comprised the joining region in all cases. The open reading frames of the partner genes MALT1, FOXP1, ODZ2, CNN3, and JMJD2C do not seem to be involved by the breakpoints, leaving the coding regions intact. The translocations are therefore similar in structure to other IGH translocations in B-cell lymphomas.

FISH with probes flanking ODZ2, JMJD2C, and CNN3 was done to confirm the breakpoints assessed from LDI-PCR. FISH confirmed LDI-PCR results in all cases (Fig. 1). Furthermore, the FISH assays were applied in all cases with known IGH rearrangement and unknown partner regions. FISH studies revealed further ODZ2 rearrangements in cases 2 and 3 and JMJD2C translocation in case 27 (Table 1). In cases 6, 7, 8, and 9 with known IGH translocation, the partner region/s remained unidentified after FISH for all known MALT lymphoma-associated genes. Taken together, we are aware of at least eight characterized translocations in MALT lymphoma (i.e., API2-MALT1, IGH-MALT1, IGH-BCL10, IGH-FOXP1, IGH-BCL6, IGH-JMJD2C, IGH-ODZ2, and IGH-CNN3), two uncharacterized translocations [i.e., t(6;7)(q25;q11) and t(1;14) (q32;q32)], and three patients with IGH translocation and unknown partner loci.

**IGH translocations lead to deregulation of partner genes.** To determine whether the novel translocations ODZ2, JMJD2C, and CNN3 are expressed/deregulated as a consequence of the juxtaposition to IGH, QRT-PCR was done. QRT-PCR showed higher expression of the rearranged genes in the index patients compared with 20 MALT lymphomas, 5 SmZL, 21 other B-NHLs, and 9 normal lymph nodes (Fig. 2). The index patient for ODZ2 was case 4, for JMJD2C case 26, and for CNN3 case 1. Unfortunately, no RNA for QRT-PCR was available in the remaining ODZ2- and JMJD2C-positive cases. In case 26 with translocation and up-regulation of JMJD2C, QRT-PCR showed no expression of other genes in the vicinity of JMJD2C (PTPRD, etc.).

![Fig. 1. Identification and conformation of novel translocations in MALT lymphoma. A, FISH confirms an IGH translocation in case 4 with t(5;14)(q34;q32). The dual break-apart probe for IGH shows the rearrangement of the IGH locus showing the orange signal on der(14) and the green signal on der(5), whereas the normal chromosome 14 carries the colocalization signal. B, FISH probes flanking ODZ2 show separate red and green signals confirming ODZ2 translocation in case 4. C, FISH probes flanking CNN3 show separate red and green signals confirming CNN3 translocation in case 1. D, FISH probes flanking JMJD2C show separate red and green signals confirming JMJD2C translocation in case 26. E, FISH probes flanking IGH show separate red and green signals showing IGH translocation in case 6 with normal metaphases. IGH partner is unknown in this patient.](image-url)
UHRF2, and JL33; data not shown). In case 1 with t(1;14), the CNN3 breakpoint falls only 10 Mb to BCL10. Immunohistochemistry for BCL10 was negative in this case (data not shown).

**Discussion**

Different subtypes of well-defined NHLs have been characterized by distinct recurrent chromosomal aberrations. Among the most typical examples are t(8;14)/IGH-MYC found in Burkitt’s lymphoma, t(11;14)/IGH-BCL1 in mantle cell lymphoma, and t(14;18)/IGH-BCL2 in follicular lymphoma (12). In contrast, a close association with a single rearrangement is not observed in MALT lymphoma and underlying genetic aberrations are unknown in the majority of cases (7). Among the genetic aberrations reported to occur in MALT lymphoma, the three translocations t(1;14)(p22;q32) (13), t(11;18)(q21;q21) (14, 15), and t(14;18)(q32;q21) (8) are of particular importance because they seem to be specific for or at least closely associated with the disease. The most frequent t(11;18)(q21;q21) has been studied extensively in gastric MALT lymphoma, and recently, a large series of MALT lymphomas has been screened for the translocation, providing important information on its frequency at the less common extragastric sites (16).

In the present study, we have done a detailed genetic analysis of 29 predominately extragastric MALT lymphomas, showing that the majority of cases harbored balanced rearrangements with a high incidence of IGH translocations. Interestingly, no uniform pattern was observed, but a large variety of IGH partner genes were identified. Compared with other well-defined B-NHLs, the genetic heterogeneity of MALT lymphoma as seen in our series is striking and may be related to other peculiarities of this disease, such as markedly variable frequencies in MALT lymphoma of different sites, underlying autoimmune disorder, and geographic heterogeneity (7, 17, 18). We identified 10 disparate translocations in nine different anatomic sites. The most common translocation was t(14;18)/IGH-MALT1 and comprised five different localizations in five cases. In contrast, two of three MALT lymphomas with a novel ODZ2 rearrangement arose in the skin, suggesting a possible but hitherto unidentified link between ODZ2 and cutaneous MALT lymphoma. In summary, the identification of several specific translocations in MALT lymphomas of all typical anatomic sites reinforces the validity of the MALT lymphoma concept but also indicates unique biological features of MALT lymphomas among B-NHLs.

The molecular genetics underlying the pathogenesis of MALT lymphoma are only recently being understood in detail for the three MALT-specific translocations t(1;18)/API2-MALT1, t(1;14)/IGH-BCL10, and t(14;18)/IGH-MALT1 (19). Antigen stimulation and CD40 triggering synergize in NF-κB activation through the formation of a CARMA1-BCL10-MALT1 ternary complex. BCL10 induces the oligomerization of MALT1, and activated MALT1 then induces the ubiquitination of NEMO, thereby ultimately leading to activation of the canonical NF-κB pathway (nuclear translocation of p50 and p65). The NF-κB transcription factor family is then essential for cell survival and activation. The identification of a high number of different translocations involving a large number of partner genes raises the question whether NF-κB as unifying pathway is operative in the large majority of MALT lymphomas. JMJ2C belongs to an extensive family of genes that encodes JmjC domain-containing proteins. JmjC domain was recently identified as a signature motif for enzymes that catalyze histone demethylation (20–22). Chromosomal aberrations and increased transcriptional expression of JMJ2C are associated with esophageal squamous cell
carcinoma, metastatic lung sarcomatoid carcinoma, and desmoplastic medulloblastomas (23–25). CN3 is associated with the cytokeratin but is not involved in contraction. The calponin-like repeats have been shown to stabilize the actin cytoskeleton, thus inhibiting metastatic capacity of melanoma and adenocarcinoma cells (26). In ovarian cancer, CN3 expression correlates with disease progression (27). ODZ2 encodes a large polypeptide, displaying the hallmarks of Drosophila pair-rule gene ozd (Ten-m). Drosophila Ten-m has many patterning roles throughout development. The role of ODZ2 in tumorigenesis is unknown. FOXP1, member of the “Foxp” subfamily, is characterized by a common DNA-binding domain (28). FOXP1 belongs to a family of transcription factors that takes part in a wide range of biological functions, including the control of cellular differentiation and proliferation, pattern formation, and signal transduction (29). FOXP1 is an essential participant in the transcriptional regulatory network of B lymphopoiesis (30). The t(3;14)/IGH-FOXPI translocation is recurrent in MALT lymphoma, and overexpression of FOXPI transcripts is associated with a poor clinical course (11, 31). Referring to the large number of different translocation partners with their various functions, including histone demethylation, cell motility, transcription factors and repressors, and apoptosis, the MALT lymphoma-associated translocations seem to affect diverse biological processes and different pathways.

In summary, our study expands the knowledge on the genetic and biological heterogeneity of MALT lymphomas. We have identified 10 MALT lymphoma-associated translocations. Although our study does not provide insights into oncogenic pathways involved with the various translocations, the genetic heterogeneity suggests a markedly diverse pathogenesis of MALT lymphomas. Further studies using models reflecting the human MALT lymphoma situation will be critical to the molecular understanding underlying these translocations in MALT lymphoma.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
Mucosa-Associated Lymphoid Tissue Lymphoma: Novel Translocations Including Rearrangements of ODZ2, JMJD2C, and CNN3

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