

## Genetic abnormalities in marginal zone B-cell lymphoma

Marginal zone B-cell lymphomas (MZL) have been separated into three distinct disorders by the World Health Organization (WHO) classification – primary nodal, primary splenic, and extranodal lymphoma of the mucosa-associated lymphoid tissue (MALT) type. Recently, important progress in the elucidation of the genetic mechanisms underlying the pathogenesis and disease progression of these lymphomas has been made. This is of particular importance since the detection of genetic abnormalities constitutes an important tool for establishing the diagnosis, monitoring the clinical course, and assessing the prognosis of patients with non-Hodgkin's lymphomas (NHL). Moreover, the discovery of recurrent chromosomal abnormalities is a prerequisite for the identification of the involved genes and can provide important pathophysiologic insights, as will be shown later. Only a small number of publications have described karyotypic abnormalities associated with MZL, owing in part to the difficulties in classifying these neoplasms in former times and the problems in producing analyzable metaphases. Recurrent chromosomal aberrations in MZL include trisomies of chromosomes 3, 7, 12, and 18, structural anomalies with breakpoints in 1q21 and 1p34, the t(3;14)(q27;q32), the t(6;14)(p21;q32) leading to deregulated cyclin D3 expression, deletions of the long arm of chromosome 7, the t(1;14)(p22;q32) and the closely related t(1;2)(p22;p12), the novel t(14;18)(q32;q21) involving *MLT/MALT1*, and the t(11;18)(q21;q21), which represents the most frequent structural chromosomal abnormality in extranodal MALT lymphomas. In some gastric MALT lymphomas, disease progression and high grade transformation have been linked to rearrangements of the *CMYC* gene, complete inactivation of the *P53* gene, and homozygous deletions of the *P16* gene, also referred to as *CDKN2A*, *MTS1*, or *INK4A*, respectively.<sup>1</sup>

The translocations t(11;18) and t(1;14) occur exclusively in extranodal MALT lymphomas. By contrast, a characteristic balanced translocation has not been described in nodal and splenic MZL. Splenic MZL seems to be associated with interstitial deletions of the long arm of chromosome 7, especially of the region 7q31-32, as well as trisomy 3.<sup>2</sup>

The distinct nature of MZL is underlined by the fact that genetic abnormalities characterizing other subtypes of B-cell NHL such as the t(11;14)/*BCL1* rearrangements, the t(14;18)/*BCL2* rearrangements, and the t(14;19)/*BCL3* rearrangements are remarkably absent in MZL.<sup>3,1</sup> The most relevant abnormalities, i.e. trisomy 3, the t(11;18)(q21;q21), the novel t(14;18)(q32;q21) involving *MLT/MALT1*, and the t(1;14)(p22;q32) will be discussed in the following.

### Trisomy 3

Trisomy of chromosome 3, either complete or partial, represents the most frequent numerical chromosomal abnormality in MZL (Figure 1). In three large cytogenetic studies, trisomy 3 has been detected in 60%,<sup>4</sup> 55%,<sup>5</sup> and 60%<sup>6</sup> of cytogenetically abnormal MZL. Two of these studies<sup>4,5</sup> analyzed extranodal MALT lymphomas, whereas in the series of Dierlamm *et al.*<sup>6</sup> trisomy 3 was detected with a similar frequency in extranodal, nodal, and splenic MZL. In contrast to these results, two other groups found trisomy 3 in only 15.4%<sup>7</sup> and 33.3%<sup>8</sup> of their cytogenetically abnormal MALT lymphomas.

A high prevalence of trisomy 3 in extranodal, nodal, and splenic MZL, ranging from 47% to 85%, has also been noted in several interphase fluorescence *in situ* hybridization (FISH) studies.<sup>6,9-12</sup> By contrast, in the FISH study of Ott *et al.*<sup>7</sup> trisomy 3 was observed in only 20% of 60 analyzed low-grade MALT lymphomas. Heterogeneous results concerning the prevalence of trisomy 3 have also been published for splenic MZL. The four interphase FISH studies focusing on this subject included 11,<sup>9</sup> 15,<sup>6</sup> 11,<sup>10</sup> and 19<sup>13</sup> cases and revealed trisomy 3 in, respectively, 27%, 46.6%, 18%, and 36% of cases. A recent study combining cytogenetics and FISH revealed trisomy 3 in 10 of 33 splenic MZL with clonal chromosomal abnormalities.<sup>14</sup> Whether the differences in the prevalence of trisomy 3 rely on the relatively small numbers of cases analyzed, mere technical problems, geographical variations, or differing selection criteria will have to await further studies.

Despite the high frequency of trisomy 3 in MZL, it is not specific for this lymphoma subtype. Trisomy 3 is also found in other subtypes of NHL and not seldomly represents a clonal evolution event.

The genetic mechanism by which trisomy 3 may contribute to neoplastic transformation or disease progression of MZL is not known. A gene dosage effect resulting in higher copy numbers of gene(s) potentially relevant to proliferation has been favored to explain the biological consequences underlying chromosomal trisomies. In this respect, commonly overrepresented regions and partial trisomies are of particular significance and can delineate subregions bearing pathogenetically important genes. In this issue of *Haematologica*, Gazzo *et al.*<sup>14</sup> analyzed 13 splenic and one nodal MZL cytogenetically characterized by unbalanced translocations involving chromosome 3 and different partner chromosomes. By using FISH with a panel of yeast artificial chromosome clones the commonly overrepresented region of chromosome 3 could be delineated to 3q13.32-3q29.

According to these results, two comparative genomic hybridization studies narrowed the relevant regions of overrepresentation to 3q21-23 and 3q25-29 in extranodal, nodal, and splenic MZL<sup>15</sup> (Figure 1) and to 3q23-25 in splenic MZL.<sup>16</sup> Starostik *et al.*

demonstrated, by microsatellite analysis amplifications of the region 3q27, the location of the *BCL6* gene in a considerable part of gastric diffuse large cell lymphomas and t(11;18)-negative gastric low grade MALT lymphomas.<sup>17</sup> The occurrence of *BCL6* rearrangements in some MZL along with its frequent involvement in diffuse large B-cell lymphomas arising at extranodal sites might point towards a role of this gene in the pathogenesis or disease progression of some MZL.<sup>18</sup> Further candidate genes located in the chromosomal region 3q21-29 are discussed in the paper by Gazzo *et al.*

#### Translocation t(11;18)(q21;q21)

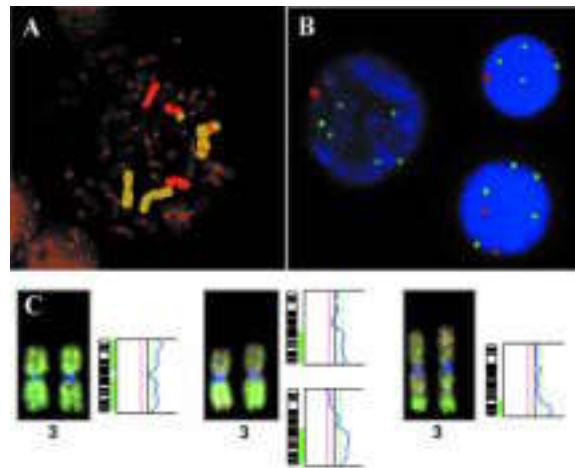
The translocation t(11;18)(q21;q21) represents the most frequent structural chromosomal abnormality in extranodal MALT lymphomas and occurs in about one third of the cases. This translocation has exclusively been described in extranodal low grade MALT lymphomas, but not in high grade MALT lymphomas or any other subtype of NHL.<sup>19-22</sup> The t(11;18)-positive MALT lymphomas reported so far involved different extranodal sites including the gastrointestinal tract, the lung, the thyroid, the orbit, and the lacrimal glands and showed a clinical spectrum ranging from localized to locally extended or disseminated disease.

In nearly all cytogenetically characterized cases, the t(11;18) occurred as the sole chromosomal abnormality, indicating that it might represent a so-called primary aberration. According to these results, Starostik *et al.* showed, by microsatellite screening of 24 gastric MALT lymphomas, that t(11;18)-positive cases rarely display secondary aberrations in contrast to t(11;18)-negative MALT lymphomas, which most frequently reveal amplifications of the region 3q26-27.<sup>17</sup>

Recent studies have also shown that the t(11;18) has important prognostic implications.<sup>23,24</sup>

Liu *et al.* investigated 111 gastric MALT lymphomas treated with antibiotics to eradicate *Helicobacter pylori*.<sup>24</sup> The t(11;18) was present in 42 (67%) of the 63 non-responsive cases, but in only two of the 48 responsive cases. Within the stage IE group, the t(11;18) was found in 26 (60%) of the 43 non-responsive cases. Thus, the t(11;18) is a reliable marker for detecting gastric MALT lymphomas that will not respond to *Helicobacter pylori* eradication treatment, including those at an early stage. Moreover, these findings indicate that the t(11;18) confers a growth advantage to MALT lymphoma cells and that the survival of the tumor cells with this translocation does not depend on immunologic stimulation mediated by *Helicobacter pylori*.

We and others have recently shown that the t(11;18) leads to a fusion of the apoptosis inhibitor gene *API2* on chromosome 11 and the novel *MLT/MALT1* gene, which encodes a human paracaspase, on chromosome 18.<sup>25-27</sup> The pathogenetic relevant event involves the derivative chromosome 11



**Figure 1.** A: FISH with library probes specific for chromosomes 3 (yellow) and 12 (red) reveals trisomy 3 with additional structural aberrations in a nodal MZL: add(3)(q28), +der(3)ins(3;12)(p21;?)ins(3;12)(q23;?), +der(12)t(3;12)(?;q22). B: FISH analysis using a cosmid probe mapped to the *BCL6* gene on 3q27 (green) and a chromosome 3 specific  $\alpha$ -satellite probe (red). In interphase nuclei, three to five green signals and two red signals can be seen in the majority of cells. These results are in accordance with the finding of overrepresentation of the chromosomal region 3q25-29 as shown by CGH in this splenic MZL (1C, right side). C: Representative partial karyotypes revealing whole or partial overrepresentation of chromosome 3 and the corresponding green-to-red fluorescence average profiles. On the left, overrepresentation of the whole chromosome 3 is evident, whereas in the middle (overrepresentation of 3q) and the right (overrepresentation of 3q25-29) only part of chromosome 3 is gained.

and leads to linkage of the three baculovirus IAP repeat (BIR) domains present in the N terminus of *API2* and a variable part of *MLT/MALT1*, which always contains the caspase p20-like domain.

*API2* belongs to the family of inhibitor of apoptosis proteins (IAP), which play an evolutionarily conserved role in regulating programmed cell death in diverse species. The *IAP* genes were first identified in baculoviruses in which they demonstrated an ability to suppress the host cell apoptotic response to viral infection. Subsequently, five human *IAP* relatives have been described: *NIAP*, *API1* (also known as *ciAP1*, *HIAP2*, *MIHB*), *API2* (*ciAP2*, *HIAP1*, *MIHC*), *XIAP/hILP* and survivin. The common structural features of all IAP family members is a motif termed baculovirus IAP repeat (BIR) occurring in one to three copies, a caspase recruitment domain (CARD) located between the BIR domain(s), and a carboxy-terminal zinc binding RING finger domain that is present in all IAPs with the exception of *NIAP* and survivin. The human *API1* and *API2* proteins were originally identified as proteins that are recruited to the cytosolic domain of the tumor necrosis factor (TNF) receptor II via their association with the TNF-associated factor (TRAF)

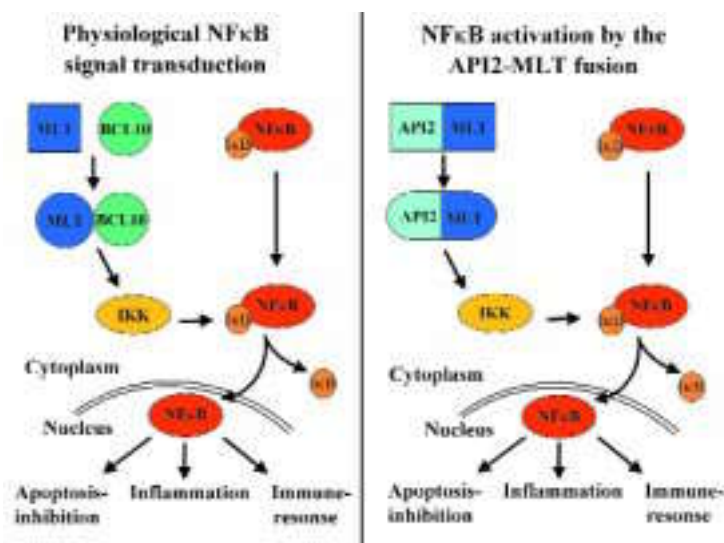


Figure 2. On the left, physiological activation of NFκB by binding of BCL10 and MLT/MALT1 is illustrated. The BCL10-MLT complex activates the IK kinase (IKK) and leads to an increased translocation of NFκB into the nucleus. NFκB induces the transcription of several genes, including those involved in apoptosis, inflammation, and immune responses. The same pathway can be activated by the API2-MLT fusion occurring in MALT lymphomas, as shown on the right.

proteins, TRAF-1 and TRAF-2, and have been subsequently shown to suppress different apoptotic pathways by inhibiting distinct caspases, such as caspase-3, caspase-7, and pro-caspase-9.<sup>28</sup>

The other gene rearranged by the t(11;18), *MLT/MALT1*, possesses a death domain, two adjacent immunoglobulin-like C2-type domains, and a caspase-like domain. Uren *et al.* have recently identified *MLT/MALT1* as a *paracaspase*, a caspase-like-protease found in several species.<sup>29</sup> Under physiologic conditions BCL10 and MLT/MALT1 form a tight complex that serves to oligomerize and activate the caspase-like domain of MLT/MALT1 leading to activation of the transcription factor NFκB (Figure 2).<sup>29,30</sup> Similarly, the fusion protein resulting from the t(11;18) significantly increases NFκB activation (Figure 2). Truncated versions of the fusion fail to activate NFκB, suggesting that both the BIR domains contributed by API2 and the paracaspase domain of the chimeric protein are required for complete activation of NFκB.<sup>29</sup> Unlike wildtype MLT/MALT1, which appears to be dependent upon an interaction with BCL10 as a mechanism for oligomerization and auto-activation, the API2-MLT/MALT1 fusion protein may possess a mechanism for self-oligomerization, possibly due to the three BIR domains contributed by the chimera.<sup>30</sup> NFκB, a member of the REL family, plays a central role in the activation of genes involved in immunity, inflammation, and apoptosis and represents a potential pro-survival signal in B-cells. The molecular consequences of the NFκB activation by the API2-MLT/MALT1 fusion remain to be determined. Inhibition of apoptotic signaling may be relevant; alternatively, activation of the NFκB pathway may mimic engagement of the antigen receptor complex, driving antigen-independent growth and lymphoma progression.

#### Translocation t(14;18)(q32;q21)

A reciprocal t(14;18)(q32;q21) closely related to the t(11;18) has recently been identified.<sup>31</sup> As shown by fluorescence *in situ* hybridization, this novel translocation involves the *MLT/MALT1* gene and the immunoglobulin heavy chain locus. Since the breakpoints of this novel translocation are very close to the breakpoints of the t(14;18)(q32;q21) seen in follicular lymphoma, it is not possible to distinguish these two translocations by conventional cytogenetic analysis. However, the molecular consequences, *MLT/MALT1* versus *BCL2* rearrangement, and the lymphoma entities characterized by these translocations, MALT lymphoma versus follicular lymphoma, are different.

So far, the t(14;18) leading to a *MLT/MALT1* rearrangement has been detected in 4 of 4 MALT lymphomas of the liver, 3 of 11 MALT lymphomas of the skin, 3 of 8 MALT lymphomas of the ocular adnexa, and 2 of 11 MALT lymphomas of the salivary glands. By contrast, none of the analyzed gastrointestinal or pulmonary MALT lymphomas showed this translocation.<sup>31</sup> Analogous to other lymphoma-associated translocations, one may speculate that juxtaposition of the *MLT/MALT1* gene to potent enhancer and promoter elements of the immunoglobulin gene results in enhanced expression of *MLT/MALT1*. It is to be hoped that ongoing analyses will soon clarify the pathogenetic consequences of this important translocation.

#### Translocations t(1;14)(p22;q32) and t(1;2)(p22;p12)

Two other recurrent translocations, t(1;14)(p22;q32) and t(1;2)(p22;p12), occur like the t(11;18) exclusively in MALT lymphomas, but involve less than 5% of the cases. These translocations fuse the *BCL10* gene on chromosome 1p22 to an immunoglobulin

gene locus and thus deregulate BCL10 expression. All *BCL10* breakpoints thus far characterized cluster within the 5' promoter region.<sup>32,33</sup> *BCL10* is a homolog of the equine herpesvirus-2 E10 gene and, like *API2*, contains an amino-terminal CARD domain. Despite its expected oncogenic role, wildtype BCL10 is pro-apoptotic and behaves as a tumor suppressor *in vitro*, notwithstanding activation of NFκB.<sup>32,33</sup>

BCL10 was found to be highly expressed in MALT lymphomas carrying the t(1;14). Moreover, *BCL10* cDNAs from t(1;14)-positive MALT lymphomas contained a variety of mutations, mostly resulting in truncations either inside or carboxy-terminal to the CARD domain. Studies of *BCL10* CARD-truncation mutants revealed that these proteins were unable to induce death or activate NFκB, whereas C-terminal truncation mutants lost pro-apoptosis but retained NFκB activation.<sup>33</sup> Overall, *BCL10* genomic mutations occur infrequently in NHL and affect 6.7% of MALT lymphomas, 9.5% of follicular lymphomas, and 4.3% of diffuse large cell lymphomas.<sup>34</sup>

BCL10 protein is expressed primarily in the cytoplasm of normal B-cells, including marginal zone B-cells.<sup>35</sup> By contrast, BCL10 is predominantly expressed in the nuclei of MALT lymphoma cells with a t(1;14).<sup>35</sup> Moreover, up to 50% of MALT lymphomas without the translocation also express BCL10, predominantly in the nucleus.<sup>34</sup> BCL10 nuclear expression is found in a higher proportion of lymphomas with dissemination to local lymph nodes or distal sites than those confined to the gastric wall. BCL10 nuclear expression is also closely related to the presence of the t(11;18).<sup>35,36</sup>

Transgenic mice with *BCL10* linked to an immunoglobulin enhancer-containing construct showed a dramatic and specific expansion of the splenic marginal zone B-cells.<sup>37</sup> This finding suggests that wild-type BCL10 may promote B-cell growth rather than B-cell apoptosis. Studies on B-cell knockout mice further support this suggestion and have shown that *BCL10* is a positive regulator of antigen-receptor-mediated NFκB activation.<sup>38</sup> BCL10 induces NFκB activation through interaction with MLT/MALT1.<sup>29,30</sup>

These data demonstrate that two apparently independent cytogenetic events, the t(1;14) and the t(11;18), that target *BCL10* and *MLT/MALT1*, affect the same signaling pathway, the result of which is the activation of NFκB and the nuclear localization of BCL10 protein. The evaluation of the precise role of nuclear BCL10 expression, the molecular consequences of NFκB activation in MALT lymphoma, and the pathogenetic consequences of the novel t(14;18) will further improve our understanding of the pathophysiology of MZL.

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## Inside Haematologica. Prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters

Both vitamin K antagonists and low-molecular-weight heparins have been recommended for the prevention of upper extremity thrombosis in cancer patients with an indwelling long-term central venous catheter. The relative benefit-to-risk ratios of these strategies have never, however, been compared. In this issue, Mismetti and co-workers<sup>1</sup> show that warfarin at a fixed, very low dose and nadroparin at a fixed, prophylactic dose have comparable benefit-to-risk ratios in the prevention of thrombosis in the above setting. Additional papers on prevention of thrombosis have been published in this journal in the last two years.<sup>2-11</sup>

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