Mantle-cell lymphoma (MCL), a subtype of B-cell non-Hodgkin’s lymphomas (B-NHL), is usually associated with poor clinical outcome. The genetic hallmark of MCL is the translocation t(11;14)(q13;32), resulting in overexpression of cyclin D1 and deregulation of the cell cycle. The DNA damage response pathway is also frequently affected by genetic alterations, e.g. by impairment of the ATM and p53 genes. Other members of this pathway are less well studied, such as MDM2. MDM2 acts as a central negative regulator of p53, and is considered to be an oncogene. MDM2 overexpression is associated with tumor progression and predicts decreased survival in solid tumors and hematological malignancies. In MCL, a subset of cases shows increased levels of MDM2 expression, but only single cases harbor genomic gains or amplifications of the MDM2 locus. Thus, the increased MDM2 expression often remains unexplained. Recently, a single nucleotide polymorphism (SNP) in the MDM2 promoter (T309G) was found to increase the affinity of the transcription factor Sp1, leading to enhanced expression of MDM2. Several reports have linked the presence of this SNP to an increased risk and/or earlier onset of malignant tumors.

In the present study we investigated the MDM2 gene expression levels of 43 MCL samples in relationship to clinical outcome, genomic status of MDM2 and presence of MDM2 SNP309. Frozen tumor samples were obtained from the Institute of Pathology, University of Würzburg and the Hospital Clinic, University of Barcelona. Thirty-two cases showed typical and 11 blastoid morphology. The proliferation fraction was evaluated by Ki-67 staining as previously described. RNA and DNA were isolated according to standard protocols. MDM2 gene expression levels were determined by Taqman™ Real-time quantitative RT-PCR with pre-developed assays (Applied Biosystems, MDM2: Hs_00234753_m1, B2M: Hs_00187842_m1) and calculated with the $2^{-\Delta\Delta Ct}$ method, using B2M as endogenous control. MDM2 overexpression is associated with inferior survival in a series of 43 mantle cell lymphomas. MDM2 overexpression is associated with copy number gains of the MDM2 locus in single tumors, but not with the recently reported MDM2 promoter SNP309.

**Figure 1.** A. MDM2 gene expression levels in 43 MCL cases measured by real-time quantitative RT-PCR. Expression levels were calculated with the relative $2^{-\Delta\Delta Ct}$ method, using B2M as an endogenous control. Different bar colors depict the status of the SNP309 in the MDM2 promoter. Samples with a genomic copy number gain of the MDM2 locus are marked with an asterisk. Kaplan-Meier plots visualizing survival groups according to 
A. MDM2 mRNA expression (cutoff >75% percentile), and 
B. SNP309 status.

We here show that increased expression of MDM2, a negative regulator of p53, correlates with inferior survival in a series of 43 mantle cell lymphomas. MDM2 overexpression is associated with copy number gains of the MDM2 locus in single tumors, but not with the recently reported MDM2 promoter SNP309.

Increased MDM2 expression is associated with inferior survival in mantle cell lymphoma, but not related to the MDM2 SNP309

Letters to the Editor

*Haematologica* 2007; 92:574-575

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In MCL, the presence of the G allele in women showed no association with younger age of tumor onset or survival when compared to men. 36 MCL cases were further analyzed for the p53 status, and 8 of them showed p53 mutations. As previously described, p53 mutations were found to be associated with poor prognosis in our series ($p=0.036$). However, no correlation between the presence of the MDM2 SNP309 or MDM2 mRNA expression and p53 status was observed.

In conclusion, we provide evidence that besides p53 alterations, increased gene expression levels of MDM2 are directly correlated with inferior survival in MCL patients, underlining the importance of the DNA damage response pathway for the pathogenesis of MCL. In single MCL tumors, genomic gains of the MDM2 locus probably account for elevated MDM2 expression levels, while the presence of the SNP309 has no impact.

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EH and VF contributed equally to this work; EC and A.R. are co-senior authors of this study.

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Key words: mantle cell lymphoma, MDM2 expression, survival, SNP309

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Table 1. Summary of the MDM2 SNP309 status in 43 MCL cases and association with age at diagnosis, sex, histology, proliferation fraction (Ki-67) and p53 status (wt: wild-type; mut: p53 mutation).

<table>
<thead>
<tr>
<th>SNP status</th>
<th>Frequency (cases, %)</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Histology</th>
<th>Ki67</th>
<th>P53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Common</td>
<td>Blastoid</td>
</tr>
<tr>
<td>Wildtype (T/T)</td>
<td>17 (39.5%)</td>
<td>16</td>
<td>1</td>
<td>14</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Heterozygot (T/G)</td>
<td>19 (44.2%)</td>
<td>12</td>
<td>7</td>
<td>14</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Homozygot (G/G)</td>
<td>7 (16.4%)</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>G allele (T+G/G)</td>
<td>26 (60.5%)</td>
<td>17</td>
<td>9</td>
<td>18</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>10</td>
<td>32</td>
<td>11</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
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References