Aberrant promoter methylation in gastric lymphomas

Aberrant gene promoter methylation of p15, p16, p73, VHL, caspase 8, and hMLH1 was investigated in gastric mucosa-associated lymphoid tissue (MALT) and diffuse large B cell (DLBC) lymphomas, with nodal marginal zone B-cell (MZBC) counterpart of MALT and DLBC lymphomas studied in comparison. MALT and MZBC lymphomas shared similar methylation patterns, with more frequent p15 and p16 methylation than gastric/nodal DLBC lymphomas, which themselves had comparable methylation patterns. Therefore, gastric MALT appeared biologically similar to nodal MZCB lymphoma, but distinct from gastric DLBC lymphoma. Gastric DLBC is more prevalent than MALT lymphoma in our population. Our results suggested that this might not represent a higher transformation rate of the latter to the former.

Table 1. The methylation status of p15, p16, p73, VHL, caspase 8 and hMLH1 as detected by methylation-specific polymerase chain reaction in gastric DLBC and MALT lymphomas, and nodal DLBC and marginal zone B-cell lymphomas.

<table>
<thead>
<tr>
<th></th>
<th>DLBC (n=22)</th>
<th>MALT (n=25)</th>
<th>p*</th>
<th>DLBC (n=30)</th>
<th>Marginal zone BC (n=12)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>p15</td>
<td>6 (27%)</td>
<td>9 (60%)</td>
<td>0.047*</td>
<td>10 (33%)</td>
<td>5 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>p16</td>
<td>12 (55%)</td>
<td>15 (50%)</td>
<td>NS</td>
<td>11 (37%)</td>
<td>10 (83%)</td>
<td>NS</td>
</tr>
<tr>
<td>p73</td>
<td>9 (41%)</td>
<td>3 (10%)</td>
<td>0.009*</td>
<td>9 (60%)</td>
<td>7 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>VHL</td>
<td>0</td>
<td>1 (7%)</td>
<td>NS</td>
<td>0</td>
<td>3 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td>Caspase 8</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>0</td>
<td>1 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>hMLH1</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 1A: Aberrant promoter methylation appeared on the whole to be more frequent in MALT/MZBC lymphomas than in gastric or nodal DLBC lymphomas (Table 1A). The p15 gene was methylated significantly more in gastric MALT than in DLBC lymphomas, whereas the p16 and p73 genes were methylated significantly more in nodal MZBC than in DLBC lymphomas. However, the patterns of aberrant methylation were similar for gastric MALT and nodal MZBC lymphomas. This was also the case for gastric and nodal DLBC lymphomas, except for p73 which was more often methylated in the stomach (Table 1B).

This study highlights a number of interesting features. Firstly, we showed that methylation patterns were different between MALT/MZBC lymphomas and gastric/nodal DLBC lymphomas. Secondly, MALT and MZBC lymphomas shared similar methylation patterns, and gastric and nodal DLBC lymphomas also shared other similar patterns. These results suggested that gastric MALT might be biologically distinct from DLBC lymphomas, but similar to nodal MZBC lymphomas. Similarly, gastric DLBC might be biologically similar to nodal DLBC lymphomas, and different from gastric MALT lymphomas. Furthermore, aberrant gene methylation appeared to be less frequent in gastric DLBC than in MALT lymphomas. As selective demethylation of the genes analyzed in this study is not known to occur during tumor progression, our observations suggest that most of the gastric DLBC lymphomas were not transformed from MALT lymphomas. However, the results would not preclude the possibility that some DLBC lymphomas with aberrant gene methylation were actually derived from MALT lymphomas.

Another intriguing finding is the frequent methylation of p73 (~60%) in MALT/MZBC lymphomas. There are few data on p73 methylation in lymphomas. Corn et al. showed that p73 was methylated in approximately 30% of primary acute lymphoblastic leukemias and Burkitt’s lymphomas. We have also...
shown that p73 was very frequently methylated in natural killer cell lymphomas. In lymphoma cell lines, methylation of p73 correlated with down-regulation of the p73 protein, and promoter demethylation led to re-expression of p73. Interestingly, our results also showed that p73 was frequently methylated in DLBC lymphoma in the stomach but not the lymph node. The significance of this in gastric lymphomagenesis merits further investigation.

Finally, the significance of gene methylation in MALT/MZBC and DLBC lymphomagenesis will need to studied by demonstrating that methylation-induced gene suppression contributes to cellular growth dysregulation or transformation.

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References

Rapid genotyping of XbaI and MspI DNA polymorphisms of the human factor VIII gene: estimation of their combined heterozygosity in the Argentinean population

In hemophilia A, indirect analysis using factor VIII gene polymorphisms is particularly valuable to obtain rapid information for genetic counseling. Herein, we describe an alternative route to investigate two intron 22 DNA polymorphisms (XbaI and MspI) using an intragenic 12kb-long amplimer. The estimated heterozygositites on 37 haplotypes from the Argentinean population were XbaI (49%), MspI (50%), and combined XbaI+MspI (63%).

Hemophilia A (HA) is an X-linked inherited bleeding disorder due to deficiency in the coagulation factor VIII (FVIII).