Low Foxp3 expression in negative sentinel lymph nodes is associated with node metastases in colorectal cancer

Lina Matera, Sergio Sandrucci, Antonio Mussa, et al.

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fatty food, fatigue, pale tongue and thin tongue coating, and a thready pulse. All patients were adult Han Chinese living in Jiangsu province with wheat products in their diets. These patients visited Jiangsu provincial hospital of TCM between December 2002 and August 2005. The results showed that 6 out of 78 patients (7.7%) were positive for IgG AGAs, and 2 (2.6%) were positive for IgA tTGs (table 1). Total IgA measurement excluded IgA deficiency. Follow-up has demonstrated that these serologically positive patients did not want to have an invasive diagnosis by duodenal biopsy but preferred to have a gluten-free diet (GFD). In China, rice and wheat are mainly consumed as human food staples and hence it is convenient for Chinese people to switch to a GFD. In two persons (cases 3 and 5) who accepted a GFD for 1 year, diarrhoea stopped. Case 3 started to thrive and case 5 stopped losing weight.

Our serological screening demonstrated that CD might exist in Jiangsu province. This province is one of the main wheat-producing areas in China. The CD-predisposing human leucocyte antigen (HLA)-DQ alleles, accounting for ~30% of heritability in Caucasians, are not rare in Han inhabitants of this area. Their frequency of haplotypes DQA1*0501-DQB1*02 (DQ2) is 7.2% and of DQA1*03-DQB1*0302 (DQ8) is 4.7%, and the frequencies of haplotypes DQA1*02-DQB1*02 and DQA1*05-DQB1*03 together capable of encoding DQ2 in trans are 9.4% and 7.8%, respectively.6 Even though there were no serological test results, Jiang et al had reported four cases of CD by duodenal biopsy this year in Zhejiang province which is neighbour of Jiangsu. The results of our research are encouraging. Considering the increasing gluten intake,6 we might gain much new information by transracial gene mapping in non-European populations.

Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age (years)</th>
<th>AGAs (IgG U/ml)</th>
<th>tTGs (IgA U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>64</td>
<td>27.6</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>20</td>
<td>30</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>20</td>
<td>50.1</td>
<td>Negative</td>
</tr>
<tr>
<td>4 (IDDM)</td>
<td>Female</td>
<td>37</td>
<td>28.8</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>55</td>
<td>12.2</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>64</td>
<td>26.7</td>
<td>8.6</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>26</td>
<td>Negative</td>
<td>8.6</td>
</tr>
</tbody>
</table>
| Positive control | Unknown | Unknown | 69.5 | 50.9

AGA, antigliadin antibody; CD, coeliac disease; IDDM, insulin-dependent diabetes mellitus; Ig, immunoglobulin; tTG, antitissue transglutaminase antibody

In a recent commentary, Sobbanu and Le Guelvolo,1 take advantage of the account of Chaput et al2 of a new population of T regulatory (Treg) lymphocytes (CD4+) to address the more general question of whether accumulation of Tregs (both CD8+ and conventional CD4+) must be considered a prognostic factor in colorectal cancer (CRC). Tregs (Foxp3+) play a pivotal role in maintaining immune system homeostasis through their ability to suppress immunological responses, including tumour immunity against tumour-associated antigens. In their interesting commentary, Sobbanu and Le Guelvolo2 argue that the in vivo immunosuppressive effect of these cells in CRC still remains controversial. Actually, according to the available data, we believe it reasonable to state that CD4+ Tregs do not contribute to CRC escape from host immunity. While earlier studies showed a higher density of tumour-infiltrating Tregs in advanced compared with early disease,3-4 an opposite pattern was reported in later studies.5-6 Correlation of Foxp3 staining with favourable clinical outcome was also suggested7 and has recently been statistically proved in two independent studies. The first study involved 967 patients with stage II and stage III CRC, whereas in the second study patients with CRC were stratified according to their mismatch repair (MMR) status. MMR-proficient patients were further stratified according to the frequency of tumour-infiltrating Foxp3. A high frequency of Foxp3 was associated with increased 5-year survival rate.8 Concomitant high frequency of Foxp3 and tumour regression indicate that, in the context of the CRC, Tregs are not significant predictors of survival.

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The number of cases and p values

<table>
<thead>
<tr>
<th>Number of cases and pT</th>
<th>pN0</th>
<th>pN1/pN2</th>
<th>Fisher exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>FoXP3+ cells in SN &gt;10%*</td>
<td>21 (18 pT2 + 3 pT3)</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>1.385e-0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FoXP3+ cells in SN &lt;10%</td>
<td>9 (pT3)</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*The numbers of Foxp3+ cells present within the SN were counted manually in three high-powered fields (HPFs) by two independent pathologists, and a threshold of 10% Foxp3+ positive cells/HPF was selected to define a Foxp3+ positive case.
We have studied the Treg lymphocytes in the afferent lymph node. The presence of Foxp3+ cells in SNs may indicate homeostatic regulation in CRC. We share Sobhanu and Le Gouvello’s doubt regarding the prognostic value of circulating Tregs in CRC. However, instead of suggesting other blood markers, we maintain that valuable prognostic data could be obtained by refining the sites of monitoring and the interpretation of Foxp3 staining. SN Foxp3 positivity may represent both an immunological marker with the potential to detect micrometastases and a prognostic factor for CRC. Its use here confirms the emerging view that, at least in the context of CRC, Treg expression is correlated with increased tumour protection and survival and is indicative of a successful immune response taking place. We anticipate that this distinctive paradigm of tumour/peritumoural Treg infiltration in CRC will be implemented in the clinic as a predictor factor.

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