Granzyme A mRNA Expression in Mycosis Fungoides Progression

To the Editor:

In a recent issue of Blood, Oudejans et al.1 showed the presence of CD8+ granzyme B+ lymphocytes, considered to be activated cytotoxic T cells, in Hodgkin’s disease. Interestingly, the presence of a high percentage of granzyme B+ lymphocytes was found to be an unfavorable prognostic marker. This is surprising because cytotoxic lymphocytes mediated lysis of tumor cells, predominantly achieved by perforin and granzymes, is considered to be of major importance for antitumor response. Oudejans et al suggested that their findings reflect an inability of activated cytotoxic T lymphocytes to kill the malignant Hodgkin’s Reed-Sternberg cells. They speculated that certain cytokines, mainly interleukin-10 (IL-10), known to be produced by the malignant cell, could be responsible for this phenomenon, as it may induce a local T-cell anergy.

We have very recently shown IL-10 overexpression in mycosis fungoides (MF), a frequent cutaneous T-cell lymphoma. Although there is evidence for a local and systemic antitumor cell–mediated immune response, granzyme A mRNA expression was studied only in MF skin samples by in situ hybridization and was not detected. Therefore, we investigated whether cutaneous granzyme A mRNA is detectable in this non-Hodgkin’s lymphoma, by using a sensitive competitive reverse transcriptase-polymerase chain reaction (RT-PCR) technique as recently described.

Granzyme A mRNA was detectable in all cutaneous T-cell lymphoma skin samples. A stage-dependent increase of granzyme A mRNA expression was detected (Table 1). Remarkably, correlation with a stage-dependent increase of IL-10 mRNA levels was found (r = .645, P = .003). Moreover, in parallel an increase of CD3 mRNA expression, indicating increasing T-cell infiltration, was observed (Table 1). Our findings indicate that the presence of granzyme, a marker of activated cytotoxic T lymphocytes (CTL)/natural killer cells, in lymphoma is not restricted to Hodgkin’s disease. Moreover, similar to the findings in Hodgkin’s disease, granzyme expression seems to be a negative prognostic sign in MF, because a stage-dependent increase was found and advanced stages are known to have a less favorable prognosis than early stages. Finally, the concomitant increase of cutaneous IL-10 and granzyme A mRNA levels further support the hypothesis by Oudejans et al that this cytokine may be involved in the development of some kind of CTL resistance at the side of the tumor.

In contrast to Oudejans, who performed immunohistological double-staining experiments, we could not conclude from our mRNA data that CD8+ cytotoxic T cells are the source of the granzyme expression in non-Hodgkin’s lymphoma, although a T-cell source may be suggested because the CD3 mRNA levels rose in parallel. Moreover, it has been reported on the poor prognosis of granzyme B–expressing peripheral T-cell lymphomas. Remarkably, MF progression is often characterized by increasing numbers of malignant CD4+ but decreasing CD8+ T cells in the skin lesions. Therefore, the increasing granzyme levels we found may reflect such a shift in the cellular pattern of the T-cell infiltrate, if the malignant MF cell could produce granzyme. Such a scenario would be of major importance, because it may indicate the capacity of the malignant cells to induce apoptosis in antitumor immune cells and escape from immune control. Therefore, further investigations to clarify these observations should be performed.

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REFERENCES


Table 1. Expression Values (AU; mean ± SD) for Granzyme A, CD3, and IL-10 mRNA in Skin Samples

<table>
<thead>
<tr>
<th>Mycosis fungoides</th>
<th>CD3</th>
<th>Granzyme A</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch stage (n = 11)</td>
<td>387 ± 186*</td>
<td>132 ± 131</td>
<td>76 ± 73</td>
</tr>
<tr>
<td>Plaque stage (n = 5)</td>
<td>407 ± 217*</td>
<td>196 ± 135</td>
<td>140 ± 95</td>
</tr>
<tr>
<td>Tumor stage (n = 3)</td>
<td>620 ± 417</td>
<td>360 ± 200</td>
<td>283 ± 115</td>
</tr>
<tr>
<td>Pleomorphic TCL (n = 5)</td>
<td>1,337 ± 599*</td>
<td>457 ± 181</td>
<td>574 ± 591</td>
</tr>
<tr>
<td>Psoriasis (n = 7)</td>
<td>145 ± 164</td>
<td>49 ± 62</td>
<td>45 ± 16</td>
</tr>
<tr>
<td>Atopic dermatitis (n = 5)</td>
<td>147 ± 61</td>
<td>44 ± 51</td>
<td>346 ± 302*</td>
</tr>
<tr>
<td>Normal skin (n = 8)</td>
<td>64 ± 55</td>
<td>59 ± 60</td>
<td>44 ± 25</td>
</tr>
</tbody>
</table>

Abbreviation: TCL, T-cell lymphoma.

* P < .01 (Mann-Whitney test) compared with normal skin. Granzyme A and IL-10 mRNA expression of the advanced stages of MF (plaque and tumor) but not of the early (patch) stage was significantly higher than in healthy and psoriatic skin (P < .01 Mann-Whitney test).


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