Abstract: Primary Sjögren syndrome (SS) is an autoimmune disease characterized by diffuse lymphoid cell infiltrates in the salivary and lacrimal glands, resulting in symptoms of dry eye and dry mouth due to insufficient secretion. Previously, we have identified the 120 kDa \( \alpha \)-fodrin as an important autoantigen on the development of SS in both animal model and SS patients, but the mechanism of \( \alpha \)-fodrin cleavage leading to tissue destruction in SS remains unclear. In murine primary SS model, tissue-infiltrating CD4\(^+\) T cells purified from the salivary glands bear a large proportion of Fas ligand (FasL), and the salivary gland duct cells constitutively possess Fas. Infiltrating CD4\(^+\) T cells identified significant \( ^{51} \)Cr release against mouse salivary gland (MSG) cells. In vitro studies demonstrated that apoptotic MSG cells result in a specific \( \alpha \)-fodrin cleavage into 120 kDa, and preincubation with caspase-inhibitor peptides blocked \( \alpha \)-fodrin cleavage. The treatment with caspase-inhibitors in vivo prevented the development of autoimmune lesions in the salivary and lacrimal glands. Thus, an increased activity in caspase cascade may be involved in the progression of \( \alpha \)-fodrin proteolysis and tissue destruction on the development of SS.


Keywords: Sjögren’s syndrome ; autoantigen ; caspase ; apoptosis
**A**

**FasL⁺ Infiltrating cells**

<table>
<thead>
<tr>
<th></th>
<th>CD4</th>
<th>CD8</th>
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</thead>
<tbody>
<tr>
<td>Cell number</td>
<td>85.2%</td>
<td>22.5%</td>
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</table>

**B**

**Fas⁺ MSG cells**

<table>
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<tr>
<th></th>
<th>3d-Tx NFS</th>
<th>non-Tx NFS</th>
<th>C57BL/6</th>
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</thead>
<tbody>
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<td>Cell number</td>
<td>60.2%</td>
<td>51.3%</td>
<td>52.3%</td>
</tr>
<tr>
<td>Fluorescence intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Y. Hayashi et al.  
Role of caspases in Sjögren's syndrome
A

anti-Fas

0 24 48 (h)
Z-VAD DEVD E64 Leupeptin

240kD
120kD

α-fodrin

B

Caspase 1

Percent Activities

control medium anti-Fas Z-VAD DEVD

0.2 20 0.2 20 (μM)

Caspase 3

Percent Activities

control medium anti-Fas Z-VAD DEVD

0.2 20 0.2 20 (μM)