Abstract: A P-glycoprotein (P-gp) inhibitor, cyclosporin A (CsA) was found to enhance the susceptibility of multidrug resistant (MDR) cancer cells to anti-P-gp antibody-dependent cellular cytolysis (ADCC) by monocytes, but the exact mechanism is unknown. In this study, we examined whether CsA enhanced the susceptibility of MDR cells through its inhibitory effect of P-gp function by using anti-ganglioside GM2 (GM2) monoclonal antibody (Ab), KM966, instead of anti-P-gp Ab, MRK16. Monocyte-ADCC induced by both KM966 and MRK16 against P-gp positive human MDR ovarian cancer cells was significantly augmented by addition of CsA. KM966, but not MRK16, induced monocyte-ADCC against P-gp negative human ovarian cancer cells and CsA enhanced this ADCC activity, indicating that suppressive effect of P-gp function by CsA was not essential to the enhancement of ADCC. Moreover, pretreatment of tumor cells with CsA augmented their susceptibility to monocyte-ADCC irrespective of P-gp expression. Interestingly, KM966 or MRK16 induced monocyte-ADCC against various human lung cancer cells expressing either GM2 or P-gp, but CsA did not affect these ADCC. These findings suggest that CsA may enhance the susceptibility to the monocyte-ADCC of ovarian cancer cells, but not of lung cancer cells, irrespective of its suppressive effect of P-gp function. J. Med. Invest. 44 : 185-191, 1998

Key Words: multidrug resistance, P-glycoprotein, ganglioside GM2, ADCC, cyclosporin A
Isolation and culture of human monocytes

Effect of CsA on anti-GM2 Ab-dependent ADCC against MDR ovarian cancer cells

Characteristics of tumor cell lines used in this study

Analysis by flow microfluorometry

Statistical analysis

Reagents

Cell lines

ADCC assay

CMV

Statistical analysis

Conclusion

The role of CsA on ADCC of MDR cancer

S. Yano et al.
Effect of CsA on monocyte-ADCC against P-gp-negative ovarian cancer cells

Effect of pretreatment of target cells with CsA on ADCC

In the study, we investigated the effect of CsA pretreatment on the ADCC against P-gp-negative ovarian cancer cells. The cells were treated with CsA at various concentrations and then subjected to ADCC assay. The results showed that CsA pretreatment significantly enhanced the ADCC against P-gp-negative ovarian cancer cells. The optimal concentration of CsA for this effect was found to be 10 μM. Further studies are needed to elucidate the underlying mechanism of this enhancement.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Effect of CsA</th>
<th>Effect of ADCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2780</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SBC-3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RERF-LC-AI</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
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Effect of CsA on monocyte-ADCC against various lung cancer cells

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The role of CsA on ADCC of MDR cancer

S. Yano et al.

![Graphs showing ADCC of MDR cancer](image)

- **A2780**
- **SBC-3**
- **RERF-LC-MS**

**% Cytotoxicity**

- **AD10**
- **H69**
- **RERF-LC-AI**

**Ab (μg/ml)**

- **CsA**
- **Medium**

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1. **Yano et al.** The role of CsA on ADCC of MDR cancer
2. **S. Yano et al.** The role of CsA on ADCC of MDR cancer

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**Graphs showing ADCC of MDR cancer**

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in vitro and in vivo experiments. The in vitro experiments were performed on isolated adult rat hearts. The in vivo experiments were conducted on rats under anaesthesia. The results of both types of experiments were compared to determine the differences and similarities between the two approaches.

The in vitro experiments showed that the isolated heart muscle maintained a normal beat rate and rhythm, and the contractility of the muscle was preserved. The in vivo experiments also demonstrated that the heart muscle was able to maintain a normal beat rate and rhythm, and the contractility of the muscle was preserved. However, the in vivo experiments showed a slight decrease in contractility compared to the in vitro experiments.

The results of both types of experiments were compared to determine the differences and similarities between the two approaches. The in vitro experiments were found to be more reliable and consistent, while the in vivo experiments were found to be more representative of the actual situation in the body.

In conclusion, the in vitro and in vivo experiments provided valuable insights into the functioning of the heart muscle. The in vitro experiments were found to be more reliable and consistent, while the in vivo experiments were found to be more representative of the actual situation in the body.

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