Cyclosporin A restricts rotavirus infection by enhancing type 1 interferon response in infected epithelial cells in vitro and in vivo

Jintao Li
Institute of Tropical Medicine
Third Military Medical University
Chongqing, P.R.China
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Introduction

- Rotavirus infection is the major cause of deadly diarrhea of infants below 5 years old all over the world
- RV vaccines are neither globally distributed nor highly effective in some developing countries
- To date, no specific anti-rotavirus drug is available
- Cyclosporin A (CsA) has long been known to be a powerful immunosuppressive agent
- CsA can inhibit virus replication such as HCV through a Cyclosporin A dependent way
Our previous studies showed that cyclophilin A (CYPA) play a critical role for rotavirus in subverting host cells IFN-β production.

CsA, the CYPA Prolyl isomerase inhibitor, can interact with CYPA through inhibiting CYPA PPIase activity.

Thus we hypothesized that CsA may be able to suppress rotavirus replication through IFN-β signaling pathway, and therefore reduce diarrhea.

He, HY, et al. 2012, BBRC

He, HY, et al. 2013, Proteomics,
Cyclosporin A (CsA) can efficiently inhibit Wa rotavirus replication in vitro
Cyclosporin A (CsA) can inhibit Wa rotavirus replication under various conditions.
cyclosporin A (CsA) can promote IFN-β but not IFN-α expression
Effect of cyclosporin A (CsA) on the expression of the type I interferon (IFN) signaling pathway regulators
Effect of cyclosporin A (CsA) on the expression of the type I interferon (IFN) signaling pathway regulators.
Expression patterns of CYPA in Wa rotavirus infected HT-29 cells with treated with CsA
Effect of CsA on SA11 rotavirus-infected neonatal mouse model
Jejunum changes as assessed by histology using a light microscope

(A) RV+PBS group

(B) RV+Ribavirin group

(C) RV+CsA group

(D) PBS group
<table>
<thead>
<tr>
<th></th>
<th>RV+PBS group (control)</th>
<th>RV+Ribavirin group</th>
<th>RV+CsA group</th>
<th>PBS group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villi height (µm)</td>
<td>296.15±43.64</td>
<td>260.92±49.17</td>
<td>301.13±55.25</td>
<td>313.54±18.25</td>
</tr>
<tr>
<td>Crypts depth (µm)</td>
<td>35.26±2.48</td>
<td>26.54±3.21*</td>
<td>26.01±1.94*</td>
<td>30.19±1.22</td>
</tr>
</tbody>
</table>

Data represents the mean±standard deviation (SD).

*Values are significantly different at p<0.05 from control.
CsA toxicity analysis in the animal model

A

Weight (g)

Days post infection of rotavirus

- RV+CsA
- RV+Ribavirin
- RV+PBS
- PBS

B

Percent survival

Days after RV infection

- RV+CsA
- RV+Ribavirin
- RV+PBS
- PBS
CsA toxicity analysis in the animal model
CsA toxicity analysis in the animal model
Conclusions

- CsA treatment of HT-29 cells in vitro suppresses Wa rotavirus infection. Furthermore, CsA inhibited Wa rotavirus replication.
- CsA treatment restores IFN-β expression through suppressing Wa rotavirus and its proteins, not IFN-α and/or IFN-β regulatory genes.
- CsA promoted Interferon Regulatory Factor-5 (IRF-5) expression, but not IRF-1, IRF-3, or IRF-7. Additionally, CsA inhibited SOCS-1 expression, but not SOCS-2 or SOCS-3.
The antiviral effect of CsA was confirmed in an RV-infected neonatal mouse model by evaluation of antigen clearance and assessment of changes in intestinal tissue pathology.

Also, there was no significant toxicity in the dose range we used in the experiments both in vitro and in vivo. Such as no differences in T cell frequency or proliferation between the CsA- and vehicle-treated groups were observed.

CsA may be a useful candidate to develop a new anti-RV strategy, although further evaluation and characterization of CsA on RV-induced diarrhea are warranted.
• You are always welcome to ask me any questions once you have