Increased risk of bacterial, fungal and other viral infections during CMV infection: decreased cytokine production in response to Toll-like receptor ligands

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Introduction

In the solid organ transplant (SOT) setting, CMV is an immunomodulatory virus that indirectly increases the risk for bacterial, fungal and viral infections. However, the pathogenesis of this phenomenon is poorly understood.

Aim

To determine whether CMV blunts peripheral immune responses to heterologous infections using Toll-like receptor ligands.

Methods

Study design:

- SOT patients were enrolled at the end of CMV prophylaxis and prospectively followed for nine months or until documented CMV infection.
- Blood was drawn at the end of prophylaxis and at onset of CMV viremia.

Stimulation of PBMCs. 2x10^5 PBMCs were stimulated with:

TLR ligand	Concentration	Receptor	Origin
LPS (*E. coli* O111:B4)	1ug/ml	TLR4	Bacterial
PAM3CSK4	10ug/ml	TLR 1/2	
Zymosan A (*S. cerevisiae*)	10ug/ml	TLR 2/6	Fungal
poly(I:C)	50ug/ml	TLR3	Viral
R848	5ug/ml	TLR7/8	
CpG-C	50ug/ml	TLR9	

After 24h of incubation, supernatants were collected.

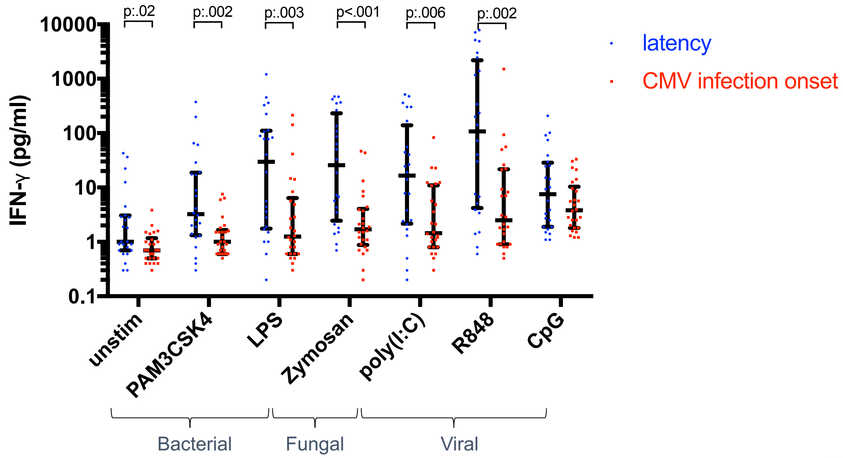
Cytokine analysis. Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon (IFN)-γ, Interleukin (IL)-1β, IL-4, IL-6, IL-10, IL-12, IFN-α2, Monocyte chemoattractant protein 1 (MCP-1) and tumor necrosis factor (TNF)-α were analysed using the Luminex™ 100 system by Eve Technologies Corp. Analyses were run in duplicate. An unstimulated specimen was used as a negative control, whereas Phytohemmaglutinin-L was used as a positive control.

Results

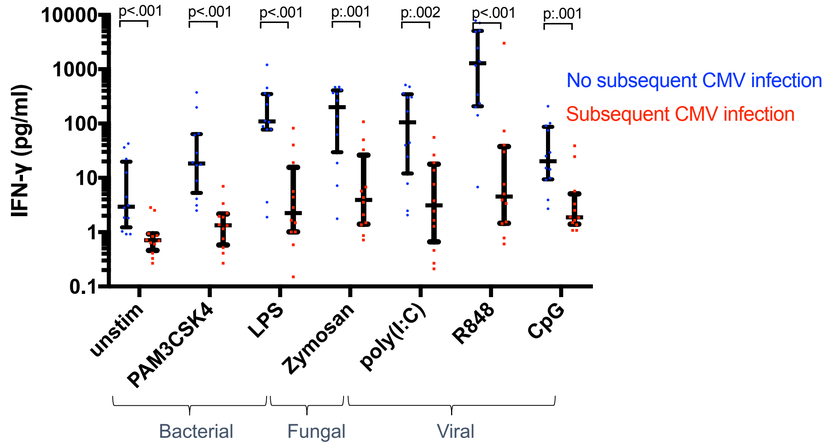
- Sixty-six specimens from 38 SOT patients were analyzed.
- Median age at SOT, was 54.1 yrs (IQR 41.1-61.8).
- Liver and lung were the most frequent transplanted organs (n=13 [34%]), followed by kidney (n=8 [21%]), heart and kidney/pancreas (n=2 [5%]).

For this poster, IFN-γ is shown as a representative cytokine.

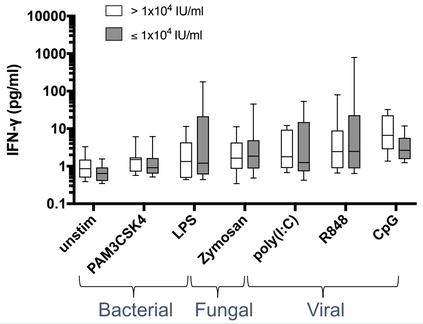
Patients have blunted responses to TLR ligands during CMV infection when compared to latency.

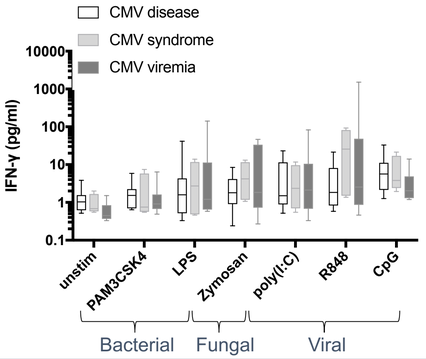


During latency, patients who will develop subsequent CMV infection have blunted responses



The blunted inflammatory responses during CMV infection are not related to the viral load at the onset of infection nor the clinical presentation of CMV infection.





Summary/Conclusions

- Responses to heterologous bacterial, viral and fungal antigens are blunted during CMV infection, suggesting a direct role of CMV on the pathogenesis of heterologous infection.
- The blunting is not related to viral load at onset of infection or by the clinical presentation of CMV infection.
- Interestingly, responses to heterologous antigens are already blunted prior to the onset of CMV infection when compared to patients who will not develop CMV infection, suggesting the possibility of alternative mechanisms independent of CMV.

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