Effect of Cytomegalovirus Infection on Immune Responsiveness

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OUTLINE

• CMV infection and vaccination responses

• Effects of CMV infection on
  – $CD8^+ T$ cell numbers
    Blood versus Lymph Nodes
  – Proteomes and Transcriptomes of differentiated $CD8^+ T$ cells
  – Markers of inflammation
CMV seropositivity decreases responses to the influenza vaccination


Daniela Frasca et al; Vaccine, 2015; 33: 1433–1439
Human Cytomegalovirus (CMV)

- CMV is a persistent β-herpesvirus affecting approximately 60% of healthy individuals
- Main tropism: white blood cells, endothelial cells
- Transmission occurs by body fluids
- Primary infection is often asymptomatic in healthy individuals
- From species origination on CMV has been within the human population (mutual adaptation)
- **Immune responses to CMV are by far the most potent anti-viral responses in humans**
Changes in CD8+ T cell subsets as a consequence of primary CMV infection after kidney transplantation

Before transplantation

1 year after transplantation

CMV-positive kidney

CMV-negative kidney

p < 0.0001

p < 0.0001

ns

ns

% of CD8+ cells

% of CD8+ cells
CMV latency induces an increase in the number of circulating CD8+ T cells
Changes induced in the lymphocyte pool by HCMV

- Appearance of high numbers of CD8+CD27− T cells with constitutive effector functions
- Increase in CD8+ T cell percentages and numbers
- Emergence of CD4+CD28−, cytolytic cells
- Expansion of Vγ2−γδ T cells
- Increase in NKG2C+ NK cells
Attrition of memory T cells

- It has been proposed that the number of memory (CD8\(^+\)) T cells in a host is inflexible, and that individual cells are constantly competing for limited space.

- Infections or vaccines that introduce over-abundant quantities of memory CD8 T cells could have detrimental consequences for the host by displacing naive cells and memory T cells specific for previous infections.

- (Especially) elderly frequently have strong expansions of (oligoclonal) CD8\(^+\) T cells that are often associated with latent cytomegalovirus infection.

Could occupation of immunological space by these cells in Lymph Nodes be contribute to low responses in CMV-infected people?
Isolation of lymph nodes from the para-iliacal area
CMV-specific CD8+ T cells have a low frequency in Lymph Nodes

Remmerswaal et al, BLOOD, 2012
In lymph nodes EBV-specific cells exceed CMV-reactive

\[ P < 0.05 \]

\[ P < 0.05 \]
Could CMV-expanded (CD8$^+$) T cells interfere with priming of naive and memory T cells in human Lymph Nodes?

Unlikely,

CMV-specific CD8$^+$ T cells do not accumulate in lymph nodes and also CD4$^+$CD28$^-$ cells are largely excluded

(Havenith et al., \textit{Int Immunol}, 2014)
If not space, what about function?
Properties of CD8$^+$CD45RA$^+$CD27$^-$ T cells

- Population of resting T cells with low proliferation and low death rate (Wallace et al., J Immunol, 2004)
- Characteristic marker profile: CCR7$^-$, CD28$^-$, CD57$^+$, 2B4$^+$, CD11a$^{bright}$, GPR56, CX3CR1
- Inducible expression of IFN$\gamma$ and TNF$\alpha$, but not IL2
- Constitutive expression of perforin, granzymes A and B; direct cytolytic activity: resting effector-type cells
- Population increases with age and in situations of mild immunosuppression
Gradual proteome changes with increased T cell differentiation

Michiel van Aalderen & Maartje van den Biggelaar
Transcription factors regulated during human CMV-induced CD8+ T cell differentiation

Hertoghs et al., J Clin Invest, 2010
CMV-specific CD8\(^+\) T cells have an IFN\(\gamma\) signature

<table>
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<tr>
<th>Gene symbol</th>
<th>Accession Nr.</th>
<th>Primary CMV infection</th>
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<th>Healthy HCMV(^+) donor</th>
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Type 1 response during primary CMV infection after renal Tx

IL-18

IFN-γ

IL-12

IP-10

IL-13

CRP

n= 18
Type 1 responses during latent CMV after Tx

(A) IL-18

(B) IFNγ

(C) IL-13

(D) CRP

CMV+; n= 18
CMV-; n=18
CMV also induces systemic type 1 cytokine response in a subset of healthy individuals

CMV+; n= 37
CMV-; n= 37

Van de Berg et al., J Inf Dis, 2010
You can’t have it all?

Nolte and van Lier, J.Exp.Med., 2006
Conclusions

- The strong immune response to CMV is unlikely to restrict immunological space for naïve cells and memory cells in lymph nodes.
  - Spleen, Bone Marrow?

- In mice (Vezys et al., Nature, 2009) hyperimmunization strongly increased vaccin-specific CD8⁺ T cell numbers but preserved immunological memory and CD4, B and naïve CD8 numbers.

- Possibly, factors produced by cells specific for latent viruses (i.e. CMV) may downregulate immune responses (IFNγ)

- Is this good news for vaccination strategies in the CMV-infected elderly?
  - Adjuvants?
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CMV-induced, effector type T cells also express CXCR3 (= IP10 receptor)

> CMV-induced effector-type CD4+ and CD8+ T cells have chemokine receptors that allow them to migrate to stimulated endothelium