Immunomodulation During Herpesvirus Latency

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The Human Herpesviruses: Lifelong Latency and Recurrent Disease

• Alpha:
  – HSV1: recurrent cold sores
  – HSV2: recurrent genital sores
  – VZV: chicken pox and shingles

• Beta:
  – CMV: severe birth defects
  – HHV6 & HHV7: rash in newborns

• Gamma:
  – EBV: mononucleosis, lymphoma
  – KSHV: Kaposi’s sarcoma
Stages of Infection with Herpesviruses

- **Acute Infection**
  - Viral Replication
  - Phase of immune response: Innate→Adaptive Response
  - Effect on host: Mild or no illness

- **Latent Infection**
  - T cells, B cells
  - Phase of immune response: Resting Memory
  - Effect on host: Presumed Inconsequential

Limit of detection
Stages of Infection with Herpesviruses

**Viral Replication**

**Acute Infection**
- Time
- Limit of detection
- T cells, B cells
- Chronic lymphocyte activation
- Reactivation attempts detected and inhibited

**Latent Infection**
- Phase of immune response:
- Innate→Adaptive Response
- Effect on host:
- Mild or no illness

Effect on host:

Phase of immune response:

Innate→Adaptive Response
Stages of Infection with Herpesviruses

- **Acute Infection**: Mild or no illness
- **Latent Infection**: T cells, B cells
- **Reactivation**: Chronic lymphocyte activation

- **Limit of detection**: Viral Replication
- **Time**: 
  - Innate → Adaptive Response
  - Chronic lymphocyte activation
  - Reactivation attempts detected and inhibited

- **Phase of immune response:**
  - Innate Response
  - Adaptive Response

- **Effect on host:**
  - Mild or no illness
  - Severe Disease

- **Immune Compromise**:
Stages of Infection with Herpesviruses

**Viral Replication**

- **Acute Infection**
  - Innate → Adaptive Response
  - Effect on host: Mild or no illness

- **Latent Infection**
  - Chronic lymphocyte activation
  - Reactivation attempts detected and inhibited

**Phase of immune response:**

- **Limit of detection**

**T cells, B cells**

**Time**

**Consequences for host response to other antigens?**

Soluble inflammatory mediators produced
Immune Modulation During Herpesvirus Latency

Latent infection
\[ \downarrow \]
Chronic, low-level viral antigen presentation
\[ \downarrow \]
Inflammatory response controls reactivation

Detrimental?
- Tissue remodeling/fibrosis
- Exacerbation of pre-existing autoimmunity
- Proliferation, mutagenesis, and cellular transformation
Beneficial?
- “Cross-protection” from heterologous infections
- Enhanced immune surveillance of pre-cancerous cells
- Prevention of allergy or autoimmunity: the “hygeine hypothesis”

Detrimental?
- Tissue remodeling/fibrosis
- Exacerbation of pre-existing autoimmunity
- Proliferation, mutagenesis, and cellular transformation

Latent infection
↓
Chronic, low-level viral antigen presentation
↓
Inflammatory response controls reactivation
Murine Herpesviruses Models of Latent Infection

- **β**: Murine cytomegalovirus (MCMV)
  - related to human CMV
- **γ**: Murine gammaherpesvirus 68 (MHV68, also γHV68)
  - related to EBV and KSHV

- Acute infection followed by lifelong latency
- Routes of spread, tropism, and pathogenesis resemble those of human viruses
Does Latent Herpesvirus Infection Protect the Host from Lethal Bacterial Infection?

MHV68 i.n.

Listeria monocytogenes, i.p.

MHV68: 1 week pi

MHV68: 4 weeks pi

MHV68: 12 weeks pi

Survival

p<0.0001

p=0.0038
Does Latent Herpesvirus Infection Protect the Host from Lethal Bacterial Infection?

MHV68 i.n.

Listeria monocytogenes, i.p.

MHV68: 1 week pi  4 weeks pi  12 weeks pi

Is latency induced cross-protection antigen specific?
Latent Herpesvirus Infection Protects the Host from Lethal Bacterial Infection: *Yersinia pestis*

- **Pneumonic plague model**
- **Bubonic plague model**

- *Herpesvirus latency induces broad antibacterial immunity*
- *Not antigen specific: innate resistance*
- *Mechanism?*
Latent MHV68 Infection Is Characterized by Elevated Serum Levels of IFNγ and TNFα

- Released by activated lymphocytes
- Control herpesvirus replication noncytolytically
- Activate phagocytes during bacterial infection

* $p < 0.0002$
Latent MHV68 Infection Is Associated with Activated Macrophages

Activated Macrophages
MHC-II upregulated 100-fold
Directly bactericidal \textit{ex vivo}
Latent MHV68 Infection Is Associated with Activated Macrophages

Mock

Latent (day 28)

Is latency induced cross-protection a general consequence of herpesvirus latency?

Activated Macrophages
MHC-II upregulated 100-fold
Directly bactericidal \textit{ex vivo}
Latent Infection with MHV68 or MCMV Protects the Host from *Listeria* Infection

MCMV latency also induces MHC-II upregulation on peritoneal macrophages: similar mechanism?
Stages of Infection with Herpesviruses

- **Acute Infection**
  - Viral Replication
  - T cells, B cells
  - Limit of detection
  - Innate to Adaptive Response: Mild or no illness

- **Latent Infection**
  - Chronic lymphocyte activation
  - Reactivation attempts detected and inhibited
  - Immune Compromise: Severe Disease

- **Chronic macrophage activation**

- **Cross-protection from bacterial challenge**
Stages of Infection with Herpesviruses

Viral Replication

Time

Limit of detection

Acute Infection

Latent Infection

T cells, B cells

Phases of immune response:

Innate → Adaptive Response

Chronic lymphocyte activation

Immune Compromise

Effect on host:

Mild or no illness

Reactivation attempts detected and inhibited

Severe Disease

Other enhancements of innate immunity during latency?
Natural Killer Cells Kill Infected and Transformed Cells

• Innate cytotoxic lymphocytes
• recognize stressed, infected, transformed cells
  • downregulated MHC-I (“missing self”)
  • upregulated stress-induced ligands (“altered self”)
• kill via cytotoxic granules (perforin, granzyme)
• secrete inflammatory cytokines (IFNγ)
• critical role for control of acute MCMV infection
  – not required for control of acute MHV68 infection
  – role in latent herpesvirus infection unclear
• mediate resistance to tumorigenesis in mice
• potential role in human antiviral immunity and tumor surveillance
Human, but not Murine, NK Cells Mediate Efficient Cytotoxicity Directly *ex vivo*

Does latent herpesvirus infection arm NK cells *in vivo*?
Latent MHV68 Increases Granzyme B in NK Cells

- harvest PEC
- gate on CD3·NK1.1+
- measure GzmB (IC stain)

MHV68 i.n. ~28 d

- enhanced IFNγ secretion following IL-12/IL-15 stimulation
- enhanced cytotoxicity in vitro

Mock
MHV68

% GzmB+ NK Cells

DW355, 31dpi, 10 mice/group
Latency Enhances Survival Following Challenge with a T Cell Lymphoma

- Protection requires NK cells

MHV68 i.n. ➔ 28 d ➔ Challenge with RMA-S i.p. ➔ Survival

DW338/B/C, 20 mice/grp, log rank p<0.0001
**Stages of Infection with Herpesviruses**

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  - Limit of detection

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**Phase of immune response:**
- Innate → Adaptive Response

**Effect on host:**
- Mild or no illness
- Severe Disease

**Immune Compromise**
- Protection from lethal tumor challenge

NK cell arming *in vivo*
Summary: Enhanced Innate Immunity During Herpesvirus Latency

• Latent β- and γ-herpesvirus infection in mice confers striking cross-protection from lethal bacterial infection
  – requires latent infection, lasts ~six months
  – is associated with systemic macrophage activation
  – is functional against diverse bacterial, viral, and protozoan pathogens

• MHV68 latency promotes arming of NK cells in vivo.
  – associated with increased survival in a lymphoma transfer model
  – may explain the difference between NK cell function in humans and pathogen-free mice
  – role for herpesvirus in resistance to tumorigenesis?
Herpesviruses as Benevogens?

Innate resistance to infection, neoplasia

Age (years)

0                   1                   2                  3    4                5

HHV6
HCMV
EBV
HHV7

Latency Induced Protection

Basal innate immunity:
- neonatal humans
- pathogen free mice

Innate immunity in neonatal humans and pathogen-free mice.
Significance

• Herpesvirus latency in mice upregulates the setpoint of innate immunity

• Herpesvirus latency may represent a form of co-evolved, mutualistic symbiosis
  – universal vaccination against herpesviruses may alter this balance and deprive the host immune system of critical regulatory signals

• The “normal” human immune system is shaped by chronic viral infections that do not cause clinically evident disease and are absent in pathogen-free mice.
  – There are no herpesvirus-free humans
  – A comprehensive understanding of human immunology may require animal models infected with these viral symbionts
Acknowledgements

Laboratory of Skip Virgin

• Doug White
• The Virgin Lab

Washington University Collaborators

• Yersinia: Virginia Miller & lab
• Listeria: Emil Unanue & lab
• NK arming: Todd Fehniger & Tim Ley

Purdue Collaborators

• Rebecca Doerge
• Douglas LaCount

Funding

• Cancer Research Institute postdoctoral fellowship (Barton)
• NIH research and institutional training grants
• American Cancer Society IRG
• Abbott Scholar Award

The Barton Lab, Purdue University
Biological Sciences