Role of Innate Immunity in Hepatitis B Virus Infection

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HBV Recognition by Innate Immunity

Historically, HBV seen as a “stealth” virus
  • Not visible to innate sensing

Mounting evidence for HBV recognition

Multiple pattern recognition receptors
  • TLR-2
  • CD14/TLR-4
  • RIG-I
  • cGAS

HBV Recognition by Innate Immunity

- Recognition ≠ inflammation

- Evidence HBV can inhibit signaling
  - HBV polymerase, X

- Caveat
  - Transfection systems
  - Stimuli was not HBV
  - Restricted to hepatocytes – PBMC not infected

- Infection systems may clarify

Innate Immune Response in Chronic HBV

- Vertical transmission accounts for a majority of chronically infected patients.
- Innate immune system is exposed to HBV before birth.
- No longer any acute response to HBV because virus is always present.

Innate Immune Response in Chronic HBV

- Innate immune system displays a regulatory role during chronic HBV infection
  - Suppress anti-HBV immunity
  - Regulate inflammation

- Innate immune cells dominate the immune composition of the liver
Innate Immune Regulation in Chronic HBV

- **Myeloid-derived suppressor cells (MDSC)**
  - Expanded in chronic HBV patients
  - IL-10 & arginase suppress T cells

- **Kupffer cells produce IL-10 in response to HBV core antigen**
  - Mouse model
  - Suppression of T cell immunity

- **NK cell TRAIL expression**
  - HBV-specific T cells express increased receptor for TRAIL
  - NK-mediated depletion of HBV-specific T cells

References:
A) Blocking NK TRAIL-mediated killing of HBV-specific T cells.
B) Inducing presentation of the HBV antigen depot in monocytes
C) TLR-8 activation of intrahepatic monocytes stimulating IL-12 and IL-18
D) TLR-7 mediated IFN-a production from plasmacytoid DC.
E) NKT cell recognition of CD1d on infected hepatocytes.
F) Blocking MDSC-mediated suppression
G) Direct triggering of RIG-I in infected hepatocytes
H) CpG induction of iMATEs
Blocking NK TRAIL-mediated killing of HBV-specific T cells.
Opportunities for Innate-targeted Immunotherapy

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Maini & Gehring. J. Hepatol. 64, S60–S70 (2016).
Inducing presentation of the HBV antigen depot in monocytes

GM-CSF + IL-4

6d

Monocyte-derived DC

Co-culture +/- Activation

HBsAg-specific CD8 T cell

CD14 MN

Unstim

pI:C

LPS+CD40L

IFN-\gamma spots/25,000 cells

Healthy

Chronic HBV HLA-mismatched

Chronic HBV HLA-matched

Gehring et al, J Clin Invest. 2013;123(9):3766-76
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TLR-8 activation of intrahepatic monocytes stimulating IL-12 and IL-18
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TLR-7 mediated IFN-alpha production from plasmacytoid DC.

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Blocking MDSC-mediated suppression

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Direct triggering of RIG-I in infected hepatocytes

SB9200: Spring Bank Pharmaceutical RIG-I agonist

Chronic Woodchuck Hepatitis Virus Infection model

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Maini & Gehring. J. Hepatol. 64, S60–S70 (2016).
CpG induction of iMATEs

Opportunities for Innate-targeted Immunotherapy

Multiple mechanisms that can potentially be exploited

Maini & Gehring. J. Hepatol. 64, S60–S70 (2016).
Opportunities for Innate-targeted Immunotherapy

Direct antiviral effect & potential environmental effect – permit adaptive immunity

**Concern:** Innate immunity is inherently non-specific
- Identify therapeutic window
- Effective intrahepatic immune response = inflammation
  - Control/balance systemic toxicity

- Innate immunity is playing a significant regulatory role in chronic HBV
  - What is regulating the regulators? ????

- Understanding what is controlling the negative regulation by innate immunity may permit an organic immune response vs. therapeutic boosting.