Immune response to HBV in Patients

Adam J. Gehring, Ph.D.
Biology Lead
Toronto Centre for Liver Disease
University Health Network (UHN)

Assistant Professor
Department of Immunology
University of Toronto
Adaptive Immune Response to HBV

**Acute/Resolved**

Robust, coordinated adaptive immunity
1. CD8 T cells mediate clearance of infected cells
2. B cells - anti-HBs marker of resolution
3. CD4 T helper cells support CD8 & B cells

**Chronic**

Weak Adaptive Immune response
1. Low T cell frequency
2. Lack of effective antibodies
T cell responses do not correlate with clinical stages
- Arbitrary definitions and many patients = indeterminate

Age may be better correlation of T cell immunity
- Higher T cell frequency detectable in younger patients
- Lower PD-1 expression

**Profile of the HBV-specific T cell Response in Chronic HBV**

**Variation in T cell repertoire**
- Age of patients alters antigen-specific repertoire
- Different Genotypes/HLA profiles elicit different T cell repertoires
- Important for measuring immunity
- Designing vaccines

**T cells in the liver do not equal T cells in the blood**
- Different phenotype
- Different functional profile
- Different transcription factor profile
Patients who lose HBsAg have higher T cell frequency
- HBsAg loss on nuc treatment shows T cell recovery
  - almost to level of acute response
- T cell response in spontaneous clearance is higher than untreated
- Cross-sectional study – chicken & egg?
Hepatitis B Virus Immune Evasion/Exhaustion

- **Hepatotropic virus**
  - Liver is generally a tolerizing organ
    - Hepatocyte/LSEC Antigen presentation = bad for priming
    - Suppressive Dendritic cells
    - High IL-10, TGF-β, PD-L1, enzymes degrading essential amino acids, hypoxia

- **High Antigen burden**
  - High viral load
  - High viral antigen
    - HBsAg up to 1 mg/ml in serum
    - HBc-related Ag = ?
  - Constant presentation?
    - Hepatocytes, LSEC, Periphery?
Specific Mechanisms Suppressing HBV-specific T cells

**Inhibitory receptors often co-expressed**

**Significant mitochondrial dysfunction**
- • Impairs T cell functionality
- • Antioxidants restore T cell functionality

**Active elimination of T cells**
- Activation induced apoptosis

**NK-TRAIL mediated killing of T cells**
Non-specific Mechanisms Suppressing HBV-specific T cell Function in chronic HBV

Myeloid Derived Suppressor Cells (MDSC)
- Produce Arginase and IL-10
- Suppress T cell expansion

Arginase elevated in HBV patients
- Correlates with ALT level
- Suppresses T cell proliferation & function

Regulatory cells – Treg & Breg
- frequency correlates with ALT
- produce IL-10
- Depletion in vitro can enhance CD8 expansion
Adaptive Immune Response to HBV
- What About B Cells? -

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Adaptive Immune Response to HBV
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Detection of the HBV antibody response
- Antigen > Immune Complexes > anti-HBs
- Immune complexes found in >90% of acute patients
- Memory anti-HBs-specific B cells detectable by elispot
  - after resolution
  - after vaccination

Memory anti-HBs-specific B cells difficult to detect
- Fewer immune complexes in chronic patients
  - mainly patients with active disease
- Correlates with activated B cell profile in patients with active disease
- IgG subclasses may be associated with better control

References:
Complexity of the Innate Immune Response to HBV

- Arguably more complex than the T cell response

- **Innate effectors**
  - NK cells, MAIT cells, γδ T cells
  - Innate effectors can be negative regulators in chronic HBV patients
  - Little data on their role in recognizing/eliminating infected hepatocytes

- **Myeloid Cells**
  - Dendritic Cells, Monocytes, Macrophages
  - Antigen presentation
  - Cytokine production

- **Parenchymal cell responses**
  - Hepatocytes, Endothelial Cells, Stellate cells

- Human innate immune response studied mainly in context of pathogenesis of chronic HBV
  - Limited data comparing innate immunity in acute - resolved – chronic HBV patients
Innate Immune Response in Chronic HBV

- Vertical transmission accounts for a majority of chronically infected patients

- No acute response to HBV because virus is always present
  - Innate immune system is exposed to HBV before birth

Alterations in the Innate Immune Response to HBV

Myeloid cell function in chronic HBV
Dendritic cell
• function highly variable
• Inhibited, activated, restored with nucleoside analogues

Monocytes
• Contain HBsAg in vivo
• No evidence of altered stimulatory capacity
• Intact cytokine production

Caveats of myeloid cell analysis
• Short-lived compared to T & B cells
• Spend few days in circulation
  • Susceptible to environmental changes
  • Bone marrow alteration?

NK cell IFN-γ production suppressed
• Related to IL-10
• Especially in hepatitis patients

Gehring J Clin Invest. 2013 Sep;123(9):3766-76
Innate Immune Response in Chronic HBV

Innate cells dominate the immune composition of the liver

**Lymphocytes**
- Blood
  - T/B cells
  - Innate Eff (NK/γδ/MAIT)
- Liver
  - T/B cells
  - Innate Eff (NK/γδ/MAIT)

**Myeloid Cells**
- Blood
  - CD14 MN
  - CD14/16 MN
  - CD16 MN
  - mDC
  - pDC
- Liver
  - CD14 MN
  - CD14/16 MN
  - CD16 MN
  - mDC
  - pDC
**Pattern Recognition receptors**

**Phase I/II Clinical Trials**
- TLR-7
- TLR-8
- Rig-I

**Pre-clinical**
- STING
- Inactivated viruses (PPOV)

**Induce innate/antiviral cytokine production**
- Cytokines: IL-1α, IL-1β, IL-10, IL-6, IL-12, IL-18, TNF-α, IFN-α, IFN-λ
- Chemokines: CXCL-8, -9, -10, Mip1a, Mip1B, MCP-1

Summary

HBV-Specific T cell response
- Not significantly different across different phases of HBV
- Repertoire varies by genotype, HLA profile and localization
- Multiple specific and non-specific mechanisms maintaining the exhausted state

B cell response
- Top level data – more work is needed
- Memory B cells are detectable in resolved/vaccinated
- So far, difficult to detect in chronic patients – need better tools
- activated profile during active disease: meaning?

Innate Immunity
- Needed to enhance T cell immunity = antigen presentation
- Significant antiviral potential if properly harnessed
- Reduced NK cell function in chronic HBV
- Negatively regulates T cell immunity = MDSC, NK-TRAIL