Restoring or replacing adaptive immunity in hepatitis B

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- MK Maini has sat on advisory boards and/or provided consultancy for Gilead Sciences, Roche, Arbutus Biopharma, Janssen, VIR Biosciences, Immunocore
Rationale for an immunotherapeutic approach

• Existing and new antivirals unlikely to be able to eliminate all traces of HBV in liver (cccDNA and integrated DNA)

• Most infected adults resolve HBV infection and maintain residual virus under successful long-term immune control –blueprint for immunotherapy

• HBV remains susceptible to immune control once chronicity established
Goal of immunotherapeutic approaches

Short-term:
• Act in tandem with antivirals to clear infected hepatocytes
  • Non-cytolytic clearance / cytolytic removal

Long-term:
• Provide robust immunosurveillance to limit viral reactivation and spread from residual cccDNA

• Provide immunosurveillance to limit carcinogenesis from integrated DNA
How to go about it: Revving / Reviving / Replacing immune responses?

**Rev-up:** inadequately triggered endogenous responses
e.g. triggering cell intrinsic immunity

**Revive and Release:** exhausted endogenous responses
e.g. checkpoint inhibitors

**Replace:** new endogenous responses
e.g. therapeutic vaccination
new exogenous responses
e.g. adoptive cell transfer, antibody infusions

Potential immunomodulatory approaches for CHB

**Cell intrinsic immunity:**
Hepatocyte-targeted IFN\(\alpha\) modifications, LTR\(\beta\) agonists
RIG-I agonists, LXR agonists, TLR agonists

**Innate/Adaptive:**
TLR-7/8/9 agonists
Immunomodulatory cytokines e.g. IL-12

**Adaptive Arm:**
Therapeutic vaccination
Checkpoint inhibition
Genetically engineered T cells or soluble TCRs
Monoclonal or bispecific antibodies
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Rational combination of immunomodulators with novel potent antivirals
Rationale for boosting HBV-specific adaptive immunity

Immunotherapeutic boosting of immune cell function

HBV-specific T cell

HBV-specific B cell

activatory

inhibitory

“exhausted immune response”

Maini and Pallett, Lancet Gastroenterol Hepatol 2018
Rationale for boosting HBV-specific adaptive immunity

Immunotherapeutic boosting of immune cell function

**FUNCTIONAL CURE**

Maini and Pallett, Lancet Gastroenterol Hepatol 2018
Therapeutic targeting of B cells in HBV?

B cells skewed: IL-10-mediated T cell suppression
Das et al JI 2012

HBsAg-specific B cells persist in blood and liver but are functionally defective
Burton et al JCI 2018

Solution:
Identification of molecular constraints on B cell immunity for specific targeting
What about humoral immunity in HBV?

Antibodies assumed to protect against re-infection

BUT

• Emerging role of humoral immunity in control of chronic viral infections
• HBV reactivation/flare risk following B cell depletion in vivo (Rituximab) underscores their critical role in ongoing viral control
Defective antibody production by HBsAg-specific B cells in CHB

Bait for ex vivo characterization of HBsAg-specific B cells

<table>
<thead>
<tr>
<th>Sample type</th>
<th>ID</th>
<th>Anti-HBs</th>
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<tbody>
<tr>
<td>Vaccinated HC</td>
<td>Vac HC 01</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Vac HC 02</td>
<td>+++</td>
</tr>
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<td></td>
<td>Vac HC 03</td>
<td>+++</td>
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<tr>
<td>Patients with CHB</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>Patient 02</td>
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<td>Patient 04</td>
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</table>

Stimulation analysis of supernatants for anti-HBs

Atypical memory B cells

CD19

HBsAg-bait

FITC

BCR

Ag

CD22

CD81

CD21

CD85j

PD-1

LAG-3

FoRL5

Atypical memory B cell

Bait for ex vivo characterization of HBsAg-specific B cells
**Therapeutic targeting of defective HBsAg-specific B cells?**

*Persistent hepatotropic viral infection drives an accumulation of atypical antigen-specific and global B cells in the blood and liver with impaired antiviral capacity*

-altered signaling, homing, survival, differentiation into plasma cells, production antiviral cytokines and anti-HBs Ab

-identification of molecular targets for boosting more effective humoral immunity for functional cure of HBV

*Burton et al JCI 2018*
HBV-specific T cells are depleted and exhausted

What vaccination/immunotherapeutic approaches can rescue defective T cell responses or prime and protect new responses?
Multiple mechanisms constrain HBV-specific T cells

Tailored approaches required to optimize HBV-specific T cell boosting

Maini and Pallett, Lancet Gastroenterol Hepatol 2018
Reducing viral antigen to boost T cell responsiveness

Approaches to potently reduce HBV viral antigen production e.g. RNAi should reduce chronic T cell over-stimulation and may partially protect new vaccine responses from exhaustion

Backes et al Vaccine 2016
Interrupting negative regulation by NK cells

NK cells act as rheostats controlling HBV-specific T cells


Can manipulation of NK cell regulation enhance T cell rescue?
Checkpoint blockade to boost T cell responsiveness

Releasing excessive co-inhibition boosts HBV-specific T cells in vitro

Checkpoint blockade boosts therapeutic vaccination responses in animal models
Checkpoint blockade to boost T cell responsiveness

**BUT:**

Non-specific T cell boosting: Will checkpoint blockade be safe enough to use in CHB?

- El-Khoueiry et al, Lancet 2017
- Gane et al, J Hep 2017 S26-27

Will blocking/deleting PD-1 drive compensatory checkpoints and senescence programmes?

- Odorizzi et al JEM 2015
- Otano et al Molecular Therapy 2018
Combination checkpoint blockade in HBV?

Role of the Coinhibitory Receptor Cytotoxic T Lymphocyte Antigen-4 on Apoptosis-Prone CD8 T Cells in Persistent Hepatitis B Virus Infection

Anna Schurich,1,2 Pooja Khanna,1,2,3 A. Ross Lopes,1 Ji Jun Han,1 Dimitra Peppa,1 Lorenzo Micco,1 Gaia Nebbia,1 Patrick T.F. Kennedy,3 Anna-Maria Geretti,2 Geoffrey Dashko,7 and Mala K. Maini1,4

Upregulation of the Tim-3/Galectin-9 Pathway of T Cell Exhausution in Chronic Hepatitis B Virus Infection

Gaia Nebbia1, Dimitra Peppa1, Anna Schurich1, Pooja Khanna1,2,3, Harsimran D. Singh5, Yang Cheng1, William Rosenberg2, Geoffrey Dashko2, Richard Gilson3, Joanne ChinNeeong3, Patrick Kennedy5, Mala K. Maini1,4
Targeting underlying HBV-specific T cell mitochondrial/metabolic/epigenetic dysfunction

Reversal of T cell mitochondrial defects with mitochondrial antioxidants
Fisicaro et al Nat Med 2016

IL-12 synergises PD-1 rescue and overcomes mitochondrial defects

Additional metabolic checkpoints? e.g. Arginine

Residual epigenetic scars cannot be reversed?
Reviving and releasing endogenous adaptive immunity

Direct immunotherapeutic approaches to restore endogenous adaptive immunity

- Checkpoint modulation eg. PD-1, CTLA-4
- Metabolic rescue
- Immunoregulatory cytokines eg. IL-12, IFNα

Therapeutic vaccination

- Reduction of antigen load eg. by siRNA
- Alllevation of NK cell or MDSC suppression of antiviral T cells

Boosting existing or de-novo HBV-specific T and B cell responses

HBV-specific CD8+ T cells
HBV-specific B cells

Maini and Burton, Nature Rev Gastro Hepatol in press
Optimising the immunogenicity of therapeutic vaccines

**Patients:**

- viraemia well-suppressed on nucleoside analogues
- on additional drugs to potently reduce HBV antigens
- relatively young/early in course of disease?
- or post-treatment interruption to boost T cells?

**Vaccine:**

- incorporating core, pol and surface antigens
- highly immunogenic heterologous prime boost
- inducing multispecific broadly cross-reactive T cells
- inducing functional B cells & neutralising antibodies
- accompanied by immunomodulation to overcome HBV-specific immune exhaustion
Replacing endogenous adaptive immunity

- HBV-specific CD8+ T cells
- TCR-rediaeted T cells
- CAR T cells
- ImmTavs
- CD3 non-specific T cell
Replacing endogenous adaptive immunity

Maini and Burton, Nature Rev Gastro Hepatol in press
Boosting immunity in HBV: will it be safe?
The trade-off between immunity and immunopathology

HBV non-cytopathic virus, liver disease is immune-mediated

Immune responses e.g. CD8 T cells mediate both protection and liver injury

Hepatic flares an inevitable result of effective immune boosting?

Need to promote non-cytolytic responses?

But also need to aim for controlled hepatocyte lysis to eliminate integrated DNA & promote cccDNA loss through hepatocyte division?
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• Minimise antigen load – need studies on extent of infected hepatocytes
• Select patients with good liver reserve
• Focus immune boosting within the liver & on HBV-specific T & B cells
• Develop adjunctive approaches to limit collateral damage
Compartmentalised intrahepatic virology and immunology

For monitoring and optimising HBV functional cure strategies – liver sampling useful for detection of:

• viral reservoirs: cccDNA & integrated DNA

• liver-resident NK cells - not in blood, Stegmann et al Sci Rep 2016

• other immune cells enriched/altered in liver e.g. MAITs

• HBV-specific T cells - mostly compartmentalised in liver

• liver-resident T cells - not in blood, Pallett et al JEM 2017
  – persistent local sentinels with non-cytolytic antiviral function
  – therapeutic goal for maintenance of frontline immunosurveillance
Fine needle aspirates for HBV functional cure trials

- Liver biopsies being replaced by non-invasive monitoring
- Alternative less invasive method for sampling compartmentalized hepatic virology & immunology?

Fine needle aspirates:
- Parallel sampling liver-resident immune responses & hepatocytes to assess host/pathogen interactions at the site of disease
- Longitudinal monitoring to assess local responses to optimise functional cure trials

Gill et al, Gut Apr 2018, Gill, Pallett et al, Gut Nov 2018
Moving forward: approaches for HBV immunotherapy

- Multiple aspects of immunity to HBV defective in chronic infection
- Induction of robust intrahepatic immune surveillance for long-term functional cure
- A degree of liver damage likely to accompany induction of antiviral immunity
- Previously unsuccessful immunotherapies may be efficacious when combined with potent antigen reduction +/- specific immune manipulation
- Efficacy will require rationale combinations of immunological and virological approaches for different patient groups
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