Challenges and approaches for immunological cure of HBV

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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

Maini and Pallett, Lancet Gastro Hepatol 2018
Maini and Burton, Nature Rev Gastro Hepatol in press
Potential immunomodulatory approaches for CHB

**Cell intrinsic immunity:**

Hepatocyte-targeted IFNa modifications, LTRβ 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 TCRs
Monoclonal or bispecific antibodies
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**Rational combination of immunomodulators with direct-acting antivirals**
Multiple immune defects in HBV infection: Boosting cell intrinsic immunity

Limited induction of IFN-I & downstream cell-intrinsic immunity

-but HBV susceptible to these mediators

Solution:
Direct activation cell-intrinsic immunity
 e.g. RIG-I agonist, FXR agonist, TLR1/2/3 agonists
MAITs & \( \gamma\delta \)-T cells are enriched in liver - can their antiviral potential be harnessed by innate immunomodulators?

NK cells have defective IFN-\( \gamma \) production and limit adaptive immunity to HBV

**Solution:**
Selective modulation of innate effector/regulators?
e.g. TLR7/8 agonists
Considerations for developing innate immunomodulators

- Can bypass need to rescue exhausted adaptive immunity?

- Innate mediators typically short-lived
  - Need repeated administration?
  - Or conjunctive adaptive boosting for long-lasting immunosurveillance?

- Effects often not exclusively directed against infected hepatocytes
  - Difficult efficacy/toxicity balance?

- Issues with model systems for testing efficacy
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

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

B cells skewed: IL-10-mediated T cell suppression

HBsAg-specific B cells persist in blood and liver but are functionally defective

Solution: Identification of constraints on B cell immunity for specific targeting
HBV-specific T cells are depleted and exhausted

**Solution:**
First reduce viral antigen
Test additional approaches to revive and release
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

MDSC

NK cell
Optimising the immunogenicity of therapeutic vaccines

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

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

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

- CD3
- ImmTavs
- bispecific antibodies
- therapeutic mAbs
- non-specific T cell
- TCR-redirected T cells
- HBV-specific CD8+ T cells
- HBV-specific B cells
- non-specific T cell
- bispecific antibodies
- therapeutic mAbs

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
Liver Sampling in HBV Cure Trials: A vital “telescope onto the battlefield”?

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

- Viral reservoirs: cccDNA & integrated DNA
- Compartmentalised tissue-resident immune responses

**Fine needle aspirates for HBV functional cure trials:**

- 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

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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