Review

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Adaptive immunity in HBV infection

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Summary

During hepatitis B virus (HBV) infection, the presence of HBV-specific antibody producing B cells and functional HBV-specific T cells (with helper or cytotoxic effects) ultimately determines HBV infection outcome. In this review, in addition to summarizing the present state of knowledge of HBV-adaptive immunity, we will highlight controversies and uncertainties concerning the HBV-specific B and T lymphocyte response, and propose future directions for research aimed at the generation of more efficient immunotherapeutic strategies.

Keywords: Antiviral immunity; B lymphocytes; T lymphocytes; Immunodominance; T cell exhaustion.

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Introduction

Adaptive immunity forms a sophisticated branch of the immune system. Its "adaptability" consists in the capacity to undergo changes in response to the varying challenges imposed by different pathogens. During an infection, microbe-specific T and B lymphocytes increase in both number and fitness to fight the infection. Following disease resolution, immunological memory of the pathogen is maintained allowing a stronger and more rapid immune defense to be mounted should the same pathogen be encountered subsequently. Immunological memory is linked to the other fundamental feature of the adaptive immune system: antigen specificity. Through a complex mechanism of genetic recombination of genes coding for the variable regions of antigen receptors (i.e. antibodies and T cell receptors; TCR), B and T lymphocytes are generated with vast numbers of specificities that are then selected by the specific antigens. Antibodies secreted by B cells recognize conformational antigen, either binding the pathogen directly or binding the proteins secreted or expressed on the surface of infected cells. The TCR of the T lymphocyte provides critical recognition of pathogen protein fragments, known as epitopes, expressed on the surface of cells in association with major histocompatibility complex (MHC) class I or class II molecules [1]. These epitopes may be formed during the processing of pathogenic proteins that are synthesized within the cells (e.g., as it occurs for example in virus-infected cells) for presentation on MHC class I molecules (HLA-class I in humans) to the TCR of $CD8^+$ T cells [2]. Epitopes derived from the internalization of pathogens by specialized antigen presenting cells (i.e. dendritic cells, B cells, monocytes/macrophages) are presented by MHC class II molecules to the TCR of CD4 helper T cells [3] (Fig. 1). There are exceptions to this rule (i.e. a specialized sub-populations of dendritic cells can cross-present internalized antigen through MHC class-I molecules to CD8 T cells) [4], but the existence of two segregated pathways of antigen presentation ensure that CD8 T cells can discriminate between infected cells and cells that have only internalized pathogen's proteins [5].

During hepatitis B virus (HBV) infection, the process of generating a complex repertoire of virus-specific B and T cells is considered of paramount importance. While the innate branch of immunity (reviewed in the companion article of M. Maini and A. Gehring [148]) is designed for rapid viral replication control, the presence of HBV-specific antibody producing B cells and functional HBV-specific T cells (with helper or cytotoxic effects) ultimately determines HBV infection outcome. Such concepts have already been analyzed in several reviews and readers are directed to these works for a broad discussion of the causes of such differences and their clinical implications [6–9].

Nevertheless, further clarification is necessary to understand the mechanism through which HBV is capable of eluding the sophisticated adaptive immune system and persists unchecked throughout a patient's lifespan.

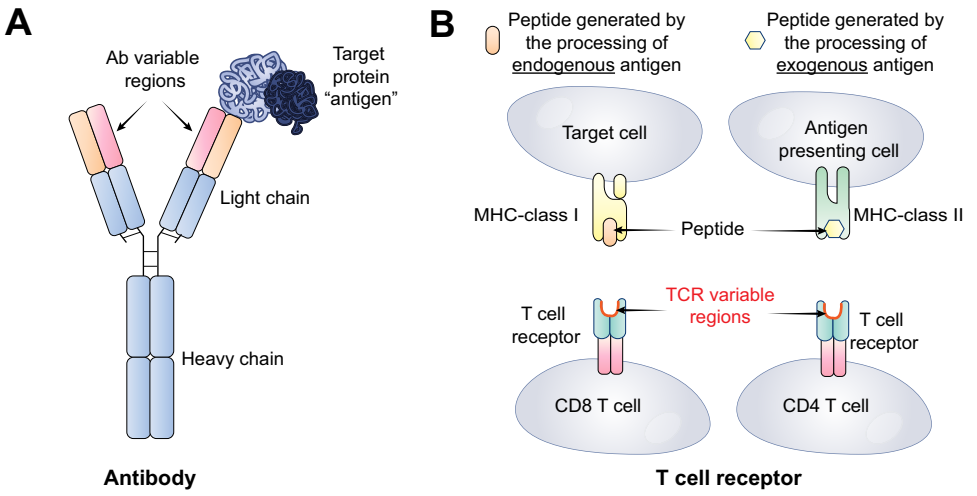

Fig. 1. Schematic representation of antibody and T cell receptor structures and their recognition ability. A schematic representation of the recognition of conformational antigen by an antibody (A) or of endogenous synthesized or exogenous captured antigen by a CD8 (cytotoxic) or CD4 (helper) T cells (B).

Key point

HBV neutralizing antibodies have a role in protection and modulation of chronic HBV infection.

Key point

Frequency and function are less characterized for HBV-specific B cells than T cells.

B cells, neutralizing antibodies and more

Over the last few decades, research into the HBV-specific B cell response has been largely neglected. Following the demonstration that distinct serum antibodies specific for different HBV proteins can be used to define different clinical groups of HBV-infected patients (reviewed in [10]), most of the research on the role of HBV-specific lymphocytes in protection and liver damage has focused on T cells instead.

Antibody responses can be elicited to the different HBV proteins (core, e, envelope, polymerase and x) and the presence or absence of these antibodies, particularly those specific for the envelope (anti-HBs) and nucleocapsid antigens (anti-HBc, anti-HBe), have been used to distinguish different clinical phases of HBV infection [10]. During an acute HBV infection, anti-HBs and anti-HBc antibodies are produced with different kinetics (Fig. 2A) but only anti-HBs detection is associated with disease resolution and virus control, while anti-HBc can coexist with a high level of HBV replication [11]. As such, while anti-HBs antibodies are considered to be protective, anti-HBc antibodies are used as a marker of ongoing or prior HBV contact. An overwhelming anti-HBc response has also been associated with acute liver damage [12].

However, the protective ability of anti-HBV antibodies was not fully elucidated until the recent discovery of the sodium-taurocholate cotransporting polypeptide (NTCP) as the HBV receptor [13,14], along with the establishment of easily infectable *in vitro* cell lines. This allowed precise mapping of HBV regions essential for infectivity to the preS1 domain and the antigenic loop region (also known as the "a-determinant") of the HBs antigen (Fig. 2B and reviewed in [15]). The preS1 domain (in particular amino acids 2–48) interacts directly with NTCP [13,14], whereas the HBs antigenic loop (residues 104–163, located between the HBs transmembrane regions I and II of the S protein) interacts with heparin sulfate proteoglycans on hepatocytes, increasing the concentration of HBV virions on the cell surface and aiding NTCP receptor interaction [16]. Antibodies against these two regions are capable of blocking HBV infection [17,18], while antibodies specific to other HBV regions not involved in HBV infectivity, such as the PreS2 region, do not show any neutralizing ability [19].

It is clear that neutralizing antibodies have a role in prevention: the presence of antibodies against the "a-determinant" region confers the protective efficacy of immunoglobulins in liver transplant patients [20] and HBV vaccination. However, because current HBV vaccines only consist of HBsAg and do not contain the preS1 region (with the enclosed 2-48 region interacting with the NTCP receptor; Fig. 2B), antibodies capable of blocking the direct interaction of HBV with its receptor cannot be produced. This is likely to be behind the induction of non-sterilizing immunity reported in vaccinated human subjects [21] and chimpanzees [22] despite the high presence of anti-HBs antibody titers. In combination with the increased detection of mutations in the a-determinant region of several HBV isolates (reviewed in [10]), this fact raises concerns regarding the rationale of targeting a single infectivity region (the a-determinant) for prophylaxis and vaccination. These concerns are heightened by a recent large epidemiological study, which revealed a substantially lower than expected vaccination efficacy in hyperendemic areas of Taiwan [23].