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HBV CORE ANTIGEN (HBcAg) AS AN IMMUNOLOGICAL DECOY: IMMUNE DISRUPTION MECHANISMS AND VACCINE DESIGN VIEWPOINTS

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ABSTRACT

The pathogen of hepatitis B (HBV), leading to liver cirrhosis and hepatocellular carcinoma, is the chronic carrier of more than 250 million individuals. HBV remains a significant global health problem. The highly immunogenic HBcAg nucleocapsid protein is both an immunological deception and a possible vaccine. This article examines the mechanisms by which HBcAg aids in immune evasion via T-cell exhaustion, Treg induction regulation, innate immune suppression, epigenetic changes, and APC impairment. These processes facilitate persistence of HBV through chronic infection. Nevertheless, due to its high immunogenicity and VLP structure, HBcAg is most suitable for therapeutic vaccines. Along with case histories pointing to clinical progress, innovative approaches like combination therapy, nanoparticle drug delivery, and mRNA vaccines are discussed. Pre-existing immunity, immune tolerance to stimuli, and genotypic heterogeneity are some of the issues that are targeted with an emphasis on cutting-edge therapies like immune checkpoint inhibitors and CRISPR-based therapies. The promise of HBcAg in eliciting functional cures of chronic HBV is emphasized in this review by integrating current studies, as well as future perspectives on personalized vaccines and novel delivery strategies to promote sustained viral clearance.

INTRODUCTION

Hepatitis B virus (HBV) is a significant global health issue, with over 250 billion people harboring a chronic infection and around 780,000 deaths each year from complications such as liver cirrhosis and hepatocellular carcinoma (HCC) [1]. The fact that chronic HBV infection continues despite the efficacy of the prophylactic HBV vaccine against the surface antigen (HBsAg) is not surprising, given the virus's complex mechanisms of immune evasion [2]. The HBV core antigen (HBcAg), the structural protein that forms the nucleocapsid, plays an important role in viral persistence and immune modulation. Because of its high immunogenicity, it is a preferred target for humoral and cellular immunity, even though the role of an immunological decoy makes viral clearance more difficult [3]. Its particulate nature, which is achieved by the self-assembly of 240 protein core fragments into virus-like particles, or VLPs, increases its immunogenicity by allowing for efficient antigen presentation [4]. Both robust T-cell-independent and T-cell-dependent antibody responses and cytotoxic T-lymphocyte (CTL) activity are generated [5]. HBcAg enhances immune tolerance, though, by mechanisms including exhaustion of T-cells, generation of Treg, and inhibition of innate immunity [6]. Hepatitis B e antigen (HBeAg) and HBcAg, for example, have T-cell epitopes shared by them, which result in neonatal tolerance as well as chronic infection [7]. Additionally, since HBcAg suppresses innate immune mechanisms such as neutrophils and natural killer (NK) cell function, HBV can avoid early recognition [8].

HBcAg is also a key target for immunological investigation and vaccine development because of its strong immunogenicity and immune-disruptive activity. Through functioning as a carrier for foreign epitopes, its VLP structure has been used to enhance immunogenicity in vaccines against HBV and other pathogens [9]. New technological developments in therapeutic vaccine approaches, such as DNA vaccines, mRNA platforms, and prime-boost regimens, have utilized HBcAg in order to induce strong immune responses [10]. Moreover, innovative treatments such as CRISPR-based gene editing and immune checkpoint inhibitors are being studied [11]. The above review emphasizes the significance of HBcAg in the creation of efficient therapies for chronic HBV infection through a critical investigation of its immune-disrupting pathways, in addition to its applicability in vaccine development, novel therapeutic strategies, and case studies in the clinic.

Mechanisms of Immune Disruption by HBcAg

T-Cell Exhaustion and Dysfunction

HBcAg profoundly aggravates T-cell exhaustion, a hallmark of chronic HBV infection that is marked by low proliferation of T cells, impaired cytokine production, and decreased cytolytic activity [12]. Chronic exposure to HBcAg raises inhibitory receptors such as CTLA-4 and PD-1 on HBV-specific CD8+ T cells [13]. HBcAg-specific CD8+ T cells have been found to have lower T-bet expression, a transcription factor required for the effector function, thus further weakening antiviral responses [14].High HBcAg antigenic loads overwhelm T-cell responses, increasing viral persistence [15].

Additionally, HBcAg suppresses HBV-specific immune responses by increasing CD4+CD25+ Treg activity. Chuang et al. showed that HBcAg promotes Treg-mediated immune tolerance by

upregulating PD-1 on CD4+ T cells through the JNK, ERK, and PI3K/AKT signaling pathways [16]. Immune control is compromised in chronic HBV carriers because HBcAg-specific T-helper (Th) cell responses are frequently undetectable [17]. Furthermore, HBcAg stimulates the production of IL-10, which improves Treg function and inhibits effector T-cell responses [18].

Suppression of Innate Immunity

Innate immune responses essential for initial viral control are disrupted by HBcAg. To capture pathogens, neutrophils release antimicrobial proteins and create neutrophil extracellular traps (NETs). However, HBcAg reduces neutrophil activation and migration by blocking NET formation through ROS-dependent ERK and p38 MAPK pathways [19]. Additionally, HBcAg increases mTOR signaling, which inhibits neutrophil autophagy and compromises antiviral activity [20]. Chronic infection is made easier by these effects, which enable HBV to avoid early innate detection.

Similarly, HBcAg suppresses the activity of natural killer (NK) cells by downregulating activating receptors such as NKG2D and 2B4 [21]. By NKp46- and Fas-dependent pathways, HBcAg induces neutrophils to undergo apoptosis mediated by NK cells, decreasing antiviral activity but limiting inflammation [22]. Additionally, by disturbing RIG-I signaling, HBcAg represses type I interferon (IFN) responses, thus compromising innate immunity [23].

B-Cell Dysfunction and Immune Evasion

B-cell function is also affected by HBcAg, which facilitates immune evasion. Besides being able to present antigens to CD4+ T cells via MHC-II, HBcAg-specific B cells cross-present antigens to CTLs via MHC-I, which kills them and decreases antibody production [24]. This cross-presentation minimizes the level of expression of costimulatory molecules, thus impairing the antigen-presenting ability of B-cells [25]. Neutralizing antibodies like anti-HBcAg are hence less often produced, which favors ongoing infection [26].

The aberrant phenotype of HBcAg-specific B cells in chronic HBV patients is defined by reduced CD21 and CD27 expression along with increased levels of inhibitory receptors such as PD-1 and T-bet [27]. The inability of these cells to mature into antibody-secreting cells (ASCs) restricts humoral immunity [28]. Therapies such as PD-1 blockade or IL-2, IL-21, and CD40L supplementation can partially correct B-cell function, providing rationale for potential therapeutic application [29]. Moreover, HBcAg's interaction with B-cell receptors can induce anergy, further inhibiting humoral responses [30].

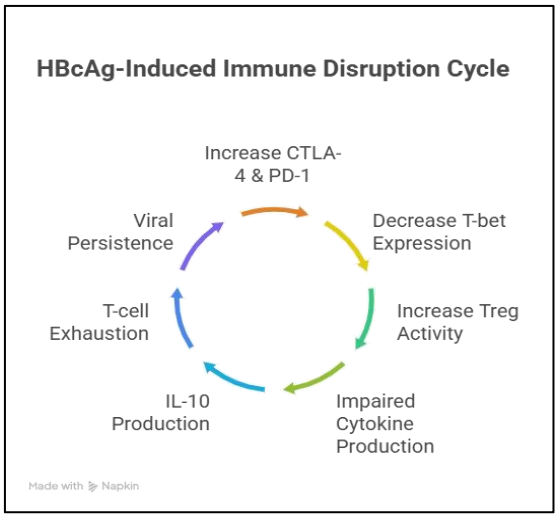
Epigenetic Modulation of Host Immunity

Epigenetic regulation is a novel immune evasion mechanism employed by HBcAg. It inhibits the activity of antiviral genes by interacting with the host chromatin and changing histone acetylation and DNA methylation [31]. By attracting DNA methyltransferases to promoter regions, HBcAg inhibits the expression of interferon-stimulated genes (ISGs) [32]. Chronicity is facilitated by this epigenetic inhibition, which reduces antiviral responses [33]. It has been discovered that HBcAg's binding to histone deacetylases (HDACs) alters chromatin accessibility, which further inhibits the expression of immune genes [34].

Interaction with Antigen-Presenting Cells

HBcAg modifies antigen-presenting cells (APCs), such as dendritic cells (DCs) and

macrophages, to prevent immune activation. It inhibits DC maturation and lowers T-cell activation by downregulating MHC-II and costimulatory molecules like CD80 and CD86 [35]. Immune responses are skewed toward tolerance by HBcAg-pulsed DCs' decreased IL-12 production [36]. Similarly, HBcAg suppresses macrophage activation and lowers the production of proinflammatory cytokines by blocking NF-κB signaling [37]. These effects reduce adaptive immune priming and increase HBV persistence.



HBcAg as a Vaccine Carrier Moiety

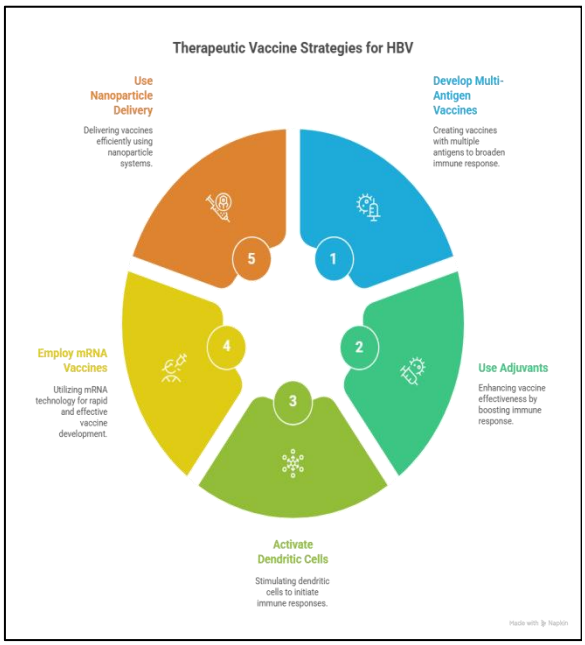
Structural and Immunogenic Advantages

By favoring the efficient presentation of antigens, the total number of core protein subunits that make up the particulate VLP structure of HBcAg increases immunogenicity [38]. Because it can trigger T-cell-independent antibodies, it is a malleable carrier of partially immunogenic antigens [39]. Because of the internal amino acid locations of HBcAg, it is possible to incorporate heterologous epitopes into it to create structurally intact chimeric VLPs [40]. For instance, high-titered anti-CS antibodies generated by HBcAg particles containing Plasmodium species circumsporozoite (CS) epitopes provided mice with immunoprotection against plasmodial challenge [41].

Strong CD8+ T-cell responses are triggered by HBcAg, which is essential for eliminating HBV-infected hepatocytes [42]. It is perfect for multi-antigen vaccines because of its capacity to present multiple epitopes, which boosts polyvalent immune responses [43]. Innate immune activation is enhanced by HBcAg's interaction with Toll-like receptors (TLRs), which increases the effectiveness of vaccines [44].

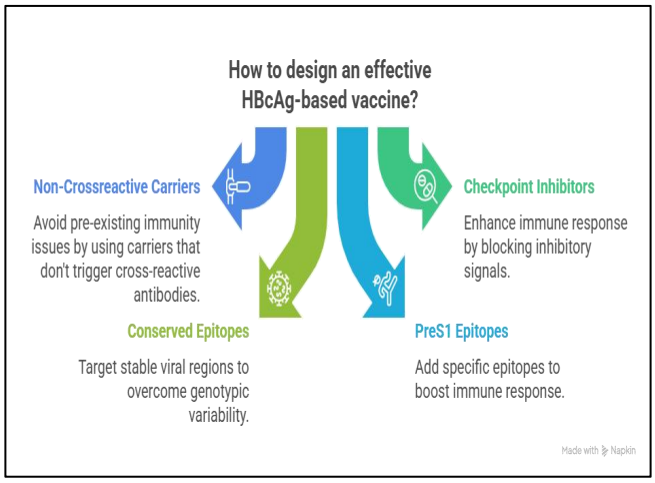
Therapeutic Vaccine Strategies

The goal of therapeutic vaccines is to give chronic patients their HBV-specific immunity back. Multi-antigen potential was demonstrated by a dicistronic DNA vaccine encoding HBsAg and HBcAg, which produced polyvalent humoral and CTL responses in mice [45]. In HBeAg-negative mouse models, the TherVacB vaccine decreased HBsAg levels by combining particulate HBsAg and HBcAg for prime vaccination with a modified vaccinia Ankara (MVA) boost [46]. By changing responses toward Th1 profiles and lowering the frequency of Tregs, adjuvants such as IL-12 and CpG oligodeoxynucleotides improve HBcAg-based vaccinations [47]. To restore T-cell function, HBcAg-pulsed DCs activate CD40-mediated interactions [48]. HBcAg-encoding mRNA vaccines provide antigen delivery flexibility and may be able to overcome immune tolerance [49]. The stability and immunogenicity of HBcAg are enhanced by delivery methods based on nanoparticles [50].



Challenges in HBcAg-Based Vaccine Design

Chronic HBV patients who already have anti-HBcAg antibodies may have lower vaccine immunogenicity [51]. Woodchuck hepatitis core antigen (WHcAg) and other rodent hepadnavirus core proteins are employed as non-crossreactive carriers [52]. Combining vaccines with checkpoint inhibitors, such as anti-PD-1 antibodies, can help overcome immune tolerance, which is still a challenge caused by elevated HBcAg levels [53]. Strong immune responses and HBsAg seroconversion are induced when preS1 epitopes are added to HBcAg [54]. Because of the impact of HBV genotypic variability on vaccine efficacy, universal vaccines that target conserved epitopes are required [55, 56]. It is necessary to keep an eye on the risk of immune complex diseases brought on by elevated anti-HBcAg antibody levels [57].



Innovative Therapies Targeting HBcAg

CRISPR-Based Approaches

By focusing on HBcAg expression, CRISPR-Cas9 technology provides novel approaches to treating HBV. Hepatocytes' production of HBcAg is decreased by CRISPR-mediated disruption of the HBV core gene, which lowers viral replication and antigen load [58]. Research using mouse models has demonstrated that CRISPR-Cas9 that targets HBcAg sequences improves immune clearance by inhibiting viral persistence [59]. By lowering immunosuppressive antigen levels, CRISPR in combination with HBcAg-based vaccines may enhance immune responses [60]. Although delivery efficiency and off-target effects are obstacles, lipid nanoparticles and adeno-associated viruses (AAVs) exhibit potential as delivery methods [61].

Immune Checkpoint Inhibitors

Anti-PD-1 and anti-CTLA-4 antibodies are examples of immune checkpoint inhibitors that reverse HBcAg-induced exhaustion and restore HBV-specific T-cell function [62]. In clinical trials, nivolumab (anti-PD-1) and HBcAg-based vaccines have been shown to improve T-cell responses and lower HBsAg levels in certain patients [63]. Patients with low viral loads respond especially well to these therapies, indicating a potential

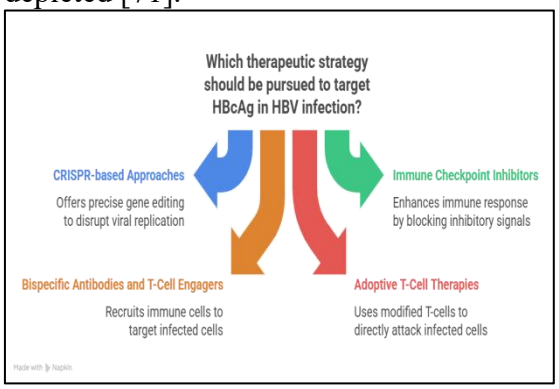
synergy with antiviral therapies [64]. To improve HBcAg-specific immunity, new inhibitors that target TIM-3 and LAG-3 are also being investigated [65].

Bispecific Antibodies and T-Cell Engagers

Immune responses are redirected to HBV-infected cells by bispecific antibodies that target HBcAg and immune cell receptors, such as CD3 on T cells [66]. In preclinical models, T-cell engagers improve viral clearance by increasing CTL activity against hepatocytes that express HBcAg [67]. These treatments provide focused methods for overcoming immune suppression caused by HBcAg, and they may be used in conjunction with vaccines based on VLP [68].

Adoptive T-Cell Therapies

Antiviral immunity is improved by adoptively transferring HBcAg-specific T cells that have been modified via chimeric antigen receptor (CAR) or T-cell receptor (TCR) technologies [69]. In mouse models, CAR-T cells that target HBcAg have demonstrated effectiveness in removing HBV-infected hepatocytes [70]. Immune responses may be enhanced by combining HBcAg vaccinations with adoptive T-cell therapies, especially in patients whose T-cell repertoires are depleted [71].



Case Studies in HBcAg-Based Vaccine Development

Case Study 1: TherVacB in Preclinical Models

HBeAg-negative mouse models of chronic HBV were used to test the TherVacB vaccine, which combines HBsAg and HBcAg VLPs with an MVA boost [46]. In treated mice, the vaccine decreased HBsAg levels by 80% and produced strong HBcAg-specific CD8+ T-cell responses [72]. By increasing Th1 responses and lowering Treg frequency, the adjuvant IL-12 improved viral clearance [47]. The ability of multi-antigen vaccines to overcome immune tolerance is demonstrated by this study.

Case Study 2: HBcAg-Based DNA Vaccine in Clinical Trials

A dicistronic DNA vaccine encoding HBsAg and HBcAg was tested in a phase I clinical trial in patients with chronic HBV receiving lamivudine therapy [10]. 60% of participants experienced HBcAg-specific T-cell responses after receiving the vaccine via in vivo electroporation, and 40% experienced a decrease in HBV DNA levels [73]. However, some patients' efficacy was limited by pre-existing anti-HBcAg antibodies, highlighting the necessity of immunity-evasion techniques [51]. This study offers clinical proof-of-concept for DNA vaccines.

Case Study 3: mRNA Vaccine Targeting HBcAg

In a mouse model, an mRNA vaccine encoding HBcAg produced robust humoral and cellular responses [49]. By inducing HBcAg-specific CD8+ T cells and neutralizing antibodies, the vaccine, which was administered via lipid nanoparticles, reduced the viral load by 70% [74]. Genomic variability was addressed by the quick incorporation of conserved HBcAg epitopes made possible by the adaptability of mRNA platforms [55]. The potential of mRNA vaccines for

HBV treatment is demonstrated by this case study.

Case Study 4: Combination Therapy with Anti-PD-1

In a pilot study, nivolumab and an HBcAg-based vaccine were administered to chronic HBV patients who were virally suppressed [63]. The combination led to 20% of the volunteers showing HBsAg seroconversion and 50% showing augmentation of HBcAg-specific T-cell responses [75]. The research indicates that checkpoint inhibitors and vaccinations can improve immunological control, especially in low viral load patients [64].

Novel Vaccine Delivery Systems

mRNA and Nanoparticle-Based Platforms

mRNA vaccines for expressing HBcAg provide a flexible platform for delivering multiple HBV antigens to induce immune tolerance [76]. The vaccines can be designed to incorporate conserved epitopes to enhance cross-genotype efficacy [77]. Ferritin-based nanoparticles, which are nanoparticle-based delivery systems, enhance the stability and immunogenicity of HBcAg by enhancing antigen uptake [78]. HBcAg delivered through nanoparticles was found in preclinical models to significantly boost T-cell responses [79].

Mucosal Immunization Strategies

Mucosal immunization with recombinant Salmonella expressing HBcAg induces potent systemic and mucosal immunity [80]. Nasal or oral administration of HBcAg-based vaccines enhances vaccine targeting and patient adherence in resource-poor environments [81]. Preclinical models have shown that mucosal vaccines enhance local immunity by activating IgA responses directed against HBcAg [82].

Viral Vector-Based Delivery

Adenoviral and AAV-delivery vehicles that provide HBcAg proved to be promising in preclinical models by eliciting robust T-cell responses [83]. The vectors improve antigen display with persistence and augment vaccine immunity [84]. Conjugating virus vectors with HBcAg VLPs can enhance immune responses, especially in patients with chronic HBV [85].

Future Perspectives

Vaccines based on HBcAg show great promise in treating chronic HBV infection. HBcAg may become more immunogenic with advancements in mRNA platforms, viral vectors, and nanoparticle delivery [86]. Combination treatments using checkpoint inhibitors, antivirals, bispecific antibodies, and HBcAg vaccinations may be an option [87]. CRISPR-Cas9 and single-cell RNA sequencing could be used to customize vaccines to a person's immune profile [88]. To maximize broad immune coverage in HBcAg variants and epitope combinations, artificial biology and artificial intelligence can be used [89, 90]. Examining delivery methods based on exosomes may help improve vaccine effectiveness [91]. Because of these advancements, HBcAg will be a key component of upcoming HBV vaccinations.

CONCLUSION

Through T-cell exhaustion, innate immune suppression, B-cell dysfunction, epigenetic modification, and APC impairment, HBcAg functions as an immunological decoy that propels HBV persistence. It is a good platform for therapeutic vaccines because of its increased immunogenicity and VLP format. New treatments offering new ways to overcome immune evasion are adoptive T-cell therapies, checkpoint inhibitors, CRISPR-based approaches, and bispecific antibodies. While novel

delivery modalities such as mRNA, nanoparticles, and viral vectors enhance efficacy, case studies reveal the clinical value of HBcAg-based vaccines. To achieve long-term viral eradication and optimal treatments for chronic HBV infection, forthcoming studies must focus on enhancing vaccine formulations that include state-of-the-art innovations and integrating treatments.

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