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A Review of The Relationship Between B Cell Phenotype and Amino Acids in the Development of Chronic Hepatitis B Progression

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A B S T R A C T

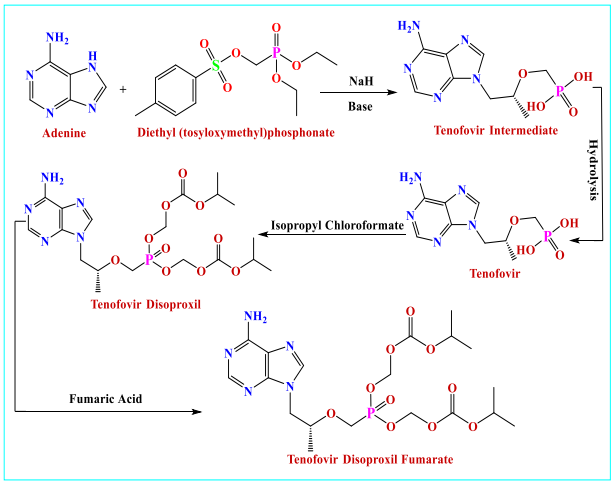
Chronic Hepatitis B (CHB) is still a major global health problem, even though there are vaccines and some antiviral treatments. The virus can stay in the liver for a long time because of its strong genetic material, which helps it escape current treatments. This study is a literature review that looks at how B cells—important immune cells—change during chronic Hepatitis B infection. It focuses on special types of B cells, like atypical memory B cells (AtM B cells) and regulatory B cells (Bregs), and how they may weaken the body's ability to fight the virus.
The review highlights gaps in current knowledge and suggests that future research should explore new ways to treat Hepatitis B by targeting these B cells. Better understanding of how B cells work in HBV infection may lead to more effective treatments and possibly a functional cure.

NOMENCLATURE	
ccDNA	closed circular DNA
CHB	Chronic Hepatitis B
TLR	Toll-like receptor
Bregs	regulatory B cells
CD	Cluster differentitation
NUC	Nucleos(t)ide analogue
NK	Natural killer cell
DLBCL	diffuse large B cell lymphoma
IL-10	interleukin-10
HCV	hepatitis C virus
AtM B cells	Atypical memory B cell

1. INTRODUCTION

One of the most serious threats to public health is HBV inspite of the availability of vaccines and antiviral medications [1-3). It is the cause of liver cancer, cirrhosis, and chronic viral hepatitis [4, 5]. Even after long-term antiviral therapy, the viral genome (the genetic material of the virus) remains in infected liver cells, meaning that the virus is not completely eliminated. When the viral genome integrates with the host genome (the genetic material of the liver cells), the stability of the cells' genome changes. This integration stops the virus from actively replicating, but it can affect the host cell, making it more difficult to eliminate the infection completely [6]. All viral gene products in HBV come from tightly closed circular DNA (cccDNA) present in the nucleus of infected liver cells. This DNA is a stable and persistent form of the viral genome, acting as a "mini-chromosome".This means that it carries all the information needed for viral replication and the production of viral proteins. cccDNA presents a

significant challenge in treatment because it remains in the nucleus of cells even after antiviral therapy, making it a continuous source of viral replication and protein production [7]. The persistence of this cccDNA is the basis for the ongoing chronic viral hepatitis [2]. Some studies have attempted to target the viral reverse transcriptase enzyme, but they have not been effective in eliminating it. As a result, researchers have explored therapeutic strategies through antiviral immune responses, aiming to eliminate or inactivate the DNA [8]. B cells have shown a role in controlling acute hepatitis B virus infection by producing antibodies against the viral surface antigen HBsAg, which is considered a therapeutic target for chronic infection [9]. However, they display signs of functional impairment and an overabundance of AtM B cells, which have high expression of inhibitory receptors such as PD-1. Consequently, this lowers B cells' ability to defend against the virus [10, 11]. Bregs have also been identified as important modulators of the immune response to HBV through Toll-like receptor (TLR) signaling [12, 13]. Although Bregs are involved in regulating immune responses and maintaining tolerance, their precise role in HBV infection remains unclear [14, 15]. The research suggests that HBcAg-specific B cells are more abundant and more capable of maturing into functional, antibody-producing cells than HBsAg-specific B cells in CHB patients, potentially playing a significant role in immune defense [16, 17]. HBcAg-specific B cells not only differ in their appearance and surface markers but also in their genetic activity, suggesting they play a unique and specialized role in the immune response against HBV compared to other memory B cells.This highlights their potential importance in HBV immunity. Additionally, elevated serum HBsAg levels are associated with increased immune inhibition and weakened HBV-specific CD4+ T cell responses, which can contribute to viral persistence and chronic infection [18]. These findings suggest that monitoring HBsAg levels may provide insights into the immune potential of HBV-infected patients and guide therapeutic interventions [19]. There are several drugs that are used for patients with viral hepatitis, including (Entecavir, Tenofovir, Interferon, Lamivudine, and Adefovir) [20, 21]. Each type has its own advantages, but the best of these drugs is Tenofovir disoproxil fumarate [TDF], which is considered safer for the kidneys and bones [22, 23]. It is prepared as follows: by reacting adenine with diethyl (tosyloxymethyl) phosphonate in the presence of a strong base such as sodium hydride (NaH). After removing the protecting groups (deprotection), the diethyl ester is converted to phosphonic acid via ester hydrolysis. Reaction with isopropyl chloroformate (Disoproxil Protection): Tenofovir reacts with isopropyl chloroformate to form tenofovir disoproxil, which improves bioabsorption. The final formulation is fumarate salt formation (the active pharmaceutical formula) [24-26]. As in Scheme [1]:



Scheme 1. Tenofovir Disoproxil Fumarate.

With an emphasis on the information gaps and prospective treatment approaches, this study attempts to investigate the role of B cell shape and function in chronic hepatitis B. This review looks at how B cells' phenotypic alterations affect the immune response to HBV. It aims to provide a thorough understanding of how these cells contribute to the infection's persistence and investigate new avenues for developing a functional cure.

2. RESEARCH METHODOLOGY

A nonsystematic narrative review was conducted to explore the role of B cell morphology and function in chronic hepatitis B [CHB]. The search was performed over a two-month period using specific keywords, including "Chronic Hepatitis B," "B Cell Morphology," "B Cell Function," "AtM B cells," and "regulatory B cells." Four reputable databases—Web of Science, PubMed, Google Scholar, and Scopus—were utilized to identify relevant literature. The initial search yielded numerous publications, which were then screened by reviewing titles and abstracts to select studies that specifically addressed the morphological and functional changes of B cells in CHB patients. Only studies that directly reported on B cell alterations in the context of chronic hepatitis B were included. To ensure the inclusion of relevant studies, the following selection criteria were applied:

- Inclusion criteria: Studies that focused on B cell morphology and function in CHB patients.
- Time frame: Studies published from 2015 to 2024 were reviewed to include the most recent findings.
- Study types: Both clinical studies and laboratory-based studies were considered,

excluding general literature reviews that did not present original data.

Full texts of the selected studies were carefully reviewed, and data were extracted and synthesized to identify consistent morphological and functional changes observed in CHB patients. These findings were then summarized and synthesized narratively. The potential for bias in study selection was considered, especially in relation to study outcomes and the inclusion of studies with specific findings.

3. DISCUSSION

3.1. Docking Molecular

The molecular docking study was conducted using the Biovia and PyRx software, using previously optimized structures and their optical analogues. The crystal structure of the protein [1qgt) was downloaded from the Protein Data Bank (PDB),27, 28 water molecules were removed, and polar hydrogen atoms were added using the PyRx computer program to demonstrate the binding strength. As **TABLE 1** shows the binding energy of the compound to the amino acids that make up the protein chain (1qgt). It also shows the upper and lower limits of the root mean square deviation (RMSD). We then used Biovia Discovery Studio to create 2D and 3D images of the amino acids bound to the drug, showing the type of bonds for each ligand. **Figure 1** illustrates the binding of the compound to the amino acids that make up the protein chain (1qgt). Among these acids are the amino acid threonine (THR), with sequence numbers (B:33) and (C:128), the amino acid serine (SER), with sequence numbers (C:121), and the amino acid leucine (LEU), with sequence numbers B:140. These acids are linked by hydrogen bonds and are colored dark green. Leucine (LEU), with sequence numbers (B:30), and isoleucine (ILE), with sequence numbers (B:105), are linked by alkyl bonds and appear light pink. The amino acids proline (PRO) with the sequence number (C:129), tyrosine (TYR) with the sequence number (C:132), and phenylalanine (PHE) with the sequence number (B:23) are linked by a (Pi-Alkyl) bond in light pink, while the rest of the amino acids appear in light green when they are molecularly bound to the protein (1qgt) by van der Waals forces. (SER- THR- VAL- PRO- TRP- PHE- ILE- TYR- ARG). **Figure 2** represents the area where hydrogen bonds were formed when the compound bonded with the amino acids of the protein (1qgt).

TABLE 1. The bonding energy of composite with amino acid

Ligand	Binding Affinity (kcal/mol)	Mode	RMSD lower bound	RMSD upper bound
1qgt_Fragment_uff_E=817.23	-8.4	0	0.0	0.0
1qgt_Fragment_uff_E=817.23	-7.6	1	1.487	2.126
1qgt_Fragment_uff_E=817.23	-7.2	2	1.97	3.364
1qgt_Fragment_uff_E=817.23	-7.0	3	4.009	8.145
1qgt_Fragment_uff_E=817.23	-6.9	4	4.361	8.411
1qgt_Fragment_uff_E=817.23	-6.5	5	16.797	19.985
1qgt_Fragment_uff_E=817.23	-6.5	6	4.09	8.206
1qgt_Fragment_uff_E=817.23	-6.4	7	16.028	19.194
1qgt_Fragment_uff_E=817.23	-6.4	8	17.401	20.613

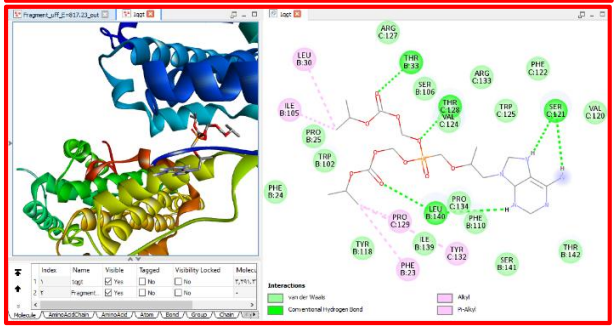


Figure 1. Shows the association of the compound with the amino acids in the protein (1qgt).

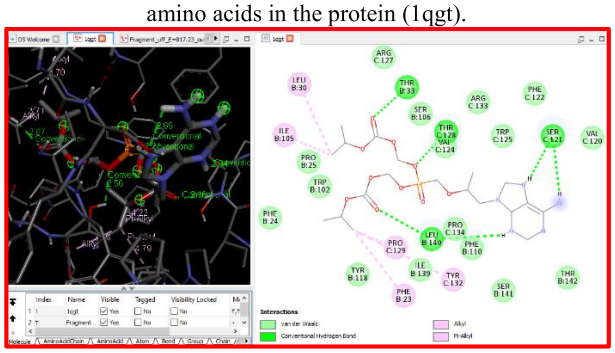


Figure 2. shows the type and length of bonds between the drug and the amino acids of the protein (1qgt).

Hydrogen bonds play an important role in the effectiveness of tenofovir as an inhibitor of hepatitis B cells. Their influence on biological activity can be summarized as follows: The presence of hydrogen bonds in tenofovir enhances its inhibitory activity against hepatitis B cells by improving binding to target enzymes,29 increasing cell permeability, and inducing cell death. Therefore, designing a drug (tenofovir) with optimal hydrogen bonding properties may lead to the development of more effective and safer anti-hepatitis therapies.30, 31.

3.2. B Cell Alterations a in Chronic Hepatitis B

3.2.1.Disruption of the CD39/CD73/Adenosine Pathway

In patients with chronic hepatitis B (CHB), B cells undergo important changes, especially in the CD39/CD73/adenosine pathway, which plays a major role in regulating immune activation. Studies have shown that patients with high levels of HBV-DNA, positive HBeAg, and elevated HBsAg tend to have reduced expression of CD39 and CD73 on circulating B

cells (27). This reduction disrupts the adenosine-mediated immune regulation, leading to excessive B cell activation and contributing to disease progression. Targeting this pathway may help restore immune balance and improve treatment outcomes.

3.2.2. Impaired Antibody Production and Functional Deficiencies

B cells in CHB also show reduced antibody production and signs of general dysfunction. This is accompanied by altered expression of important surface markers, such as a decrease in activation markers [28]. These defects limit the body's ability to fight the virus effectively. Understanding and correcting these changes could support the development of treatments that enhance B cell responses.

3.2.3 Modulation by Nucleos(t)ide Analogue Therapy

Treatment with nucleos(t)ide analogues (NUCs) not only reduces viral load but also affects B cell behavior. NUC therapy has been associated with a shift of B cells from an activated to a more resting phenotype. This change correlates with improved HBV-specific T cell responses and better immune function overall [29]. These findings suggest that NUCs may indirectly improve B cell function and contribute to viral control.

3.2.4. Cytokine Signaling and Immune Cell Interactions

B cells in CHB interact with various other immune cells and are influenced by cytokine signaling. For example, although PD-1 expression is increased on CD8+ CXCR5+ T cells, this is associated with improved B cell support and HBV-specific cytokine production [30). Additionally, cytokines such as IL-12 can influence T helper (Th) cell responses, which in turn impact B cell activity. NK cells also play a regulatory role: in CHB patients, they tend to show an inflammatory profile, but this is improved with NUC therapy, enhancing their regulatory interactions with both B and T cells [31]. These complex networks are illustrated in Figure 1.

The phenotypic and functional changes observed in B cells during CHB reflect a broader pattern of immune system disruption. Understanding how these changes affect disease progression and interact with other components of the immune system is essential for developing more effective treatments. One current limitation is the lack of direct comparison across different studies, which makes it difficult to assess the strength and consistency of the evidence. Future research should focus on uncovering the molecular mechanisms behind B cell alterations and comparing study outcomes to strengthen the scientific understanding of B cell involvement in CHB.

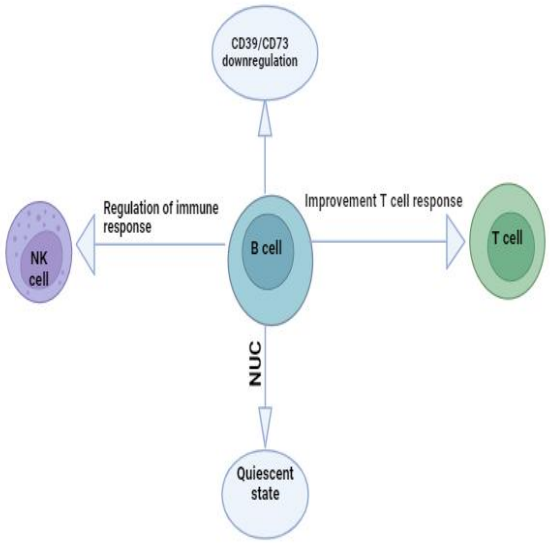


Figure 3. The diagram illustrates the regulatory role of B cells in modulating immune responses. It highlights the interactions between B cells, NK cells, and T cells, including CD39/CD73 downregulation, enhancement of T cell responses, and the induction of a quiescent state, potentially influenced by nucleos(t)ide analogues (NUC).

3.3. Physiological Alterations in B Cells Throughout CHB Stages

CHB infection is characterized by progressive changes in B cell functionality that impact the disease's progression and management. This discussion synthesizes findings from recent studies to elucidate these changes across different stages of CHB.

- **Early Stages and Acute Infection:**

In the initial stages of HBV infection, B cells are pivotal in the immunological response, engaging in antibody production and antigen presentation. However, chronic HBV infection often disrupts these functions. Early during chronic infection, B cells exhibit phenotypic and functional abnormalities, such as impaired production of HBsAg-specific antibodies and changes in cell surface markers [32].

- **Progression and Chronic Infection:**

As the disease progresses, the disruption in B cell functions becomes more pronounced. The expression of key molecules such as CD39 and CD73, which are crucial for modulating immune responses via the adenosine pathway, is often reduced in B cells from patients with high HBV DNA levels and active hepatic inflammation (33). This reduction in CD39/CD73 expression contributes to enhanced B cell activation and disease progression. Furthermore, there is an accumulation of AtM B cells and Bregs, which are associated with a compromised immune response.

These cells contribute to immune evasion and persistent viral replication by impairing effective B cell responses against HBV.

- **The Influence of Nucleos(t)ide Analog Therapy:**

Nucleos(t)ide analogue (NUC) therapy has a significant impact on B cell functionality. Treatment with NUCs can shift B cells from an activated state to a more quiescent phenotype, which is associated with improved HBV-specific T cell responses and overall immune function [34]. This modulation of B cell activity by NUCs highlights the potential for therapeutic strategies that target B cell dysfunction to enhance antiviral responses and improve clinical outcomes.

- **Advanced Stages and Complications:**

In advanced stages of chronic hepatitis B, particularly when associated with conditions like diffuse large B cell lymphoma (DLBCL), B cells undergo significant alterations. The presence of HBV can exacerbate B cell dysfunction, contributing to poor treatment outcomes and an increased risk of lymphoma [35]. HBV-associated DLBCL presents unique clinical features and necessitates careful monitoring for HBV reactivation during treatment.

- **Future Directions and Therapeutic Opportunities:**

Recognizing the specific processes underlying B cell malfunction in chronic HBV infection is crucial for developing targeted therapies. Innovative strategies are needed to address the diverse roles of B cells in HBV pathogenesis, including novel immune therapies aimed at restoring B cell function and improving antiviral responses (36). B cell dysfunction throughout the stages of CHB is marked by distinct phenotypic and functional changes that influence disease progression and therapeutic responses. Addressing these alterations through targeted treatments could improve the administration of chronic HBV infection and enhance patient outcome.

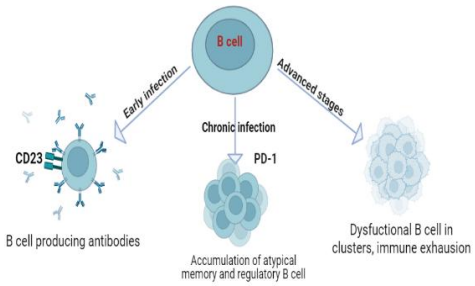


Figure 4. The figure illustrates the progression of B cell involvement during hepatitis B virus (HBV) infection across different stages of the disease. In the early infection phase, B cells engage in antibody production and antigen presentation as part of the immune response. As the infection becomes chronic, there is an accumulation of AtM B cells and Bregs cells, which contribute to immune evasion and persistent viral replication. In the advanced stages of infection, further B cell dysfunction occurs, often leading to complications and an exacerbated disease state.

3.4. Impact of Regulatory B Cells on Immune Dysfunction and Vaccine Efficacy in Chronic Hepatitis B

3.4.1. Role of Regulatory B Cells (Bregs) in Weakening Immune Response

In chronic hepatitis B (CHB), the immune system becomes unbalanced due to complex interactions between different immune cells. One important change is the increase of regulatory B cells (Bregs), especially those that produce the anti-inflammatory molecule IL-10. These Bregs can suppress the immune response by reducing the activity of HBV-specific T helper cells, which are important for fighting the virus. This weakens the body's ability to clear the infection and makes it harder to develop effective vaccines [37].

3.4.2. Bregs and Poor Vaccine Response

High levels of a specific type of Breg (CD24^hi^CD38^hi^) have been found in people who do not respond well to the hepatitis B vaccine. These people often have lower levels of protective antibodies (anti-HBs). This suggests that Bregs might be one reason why some individuals fail to develop immunity after vaccination [38].

3.4.3. Comparing HBV and HCV Infections

In hepatitis C (HCV), Bregs are also increased and linked to higher viral load and liver damage. However, unlike HBV, HCV does not cause a major increase in Tregs or Bregs. Instead, it may lead to more IL-10 production in B cells. This shows that Bregs work differently in different viral infections [39].

3.4.4. Functional Impairment of B Cells in CHB

Even though some types of B cells are more common in CHB, they often don't work properly. Studies show that these B cells have a reduced ability to make antibodies against HBV. This poor function helps the virus stay in the body and makes it harder to find a lasting cure [40]

3.5. Atypical Memory B Cells in Chronic Hepatitis B: Impaired Function and Contribution to Disease Pathogenesis

3.5.1. What Are Atypical Memory B Cells?

Atypical memory B cells (AtM B cells) are a special type of B cell that appear in many chronic infections, including chronic hepatitis B (CHB). They are different from normal memory B cells. AtM B cells have high levels of inhibitory markers like PD-1 and FCRL5 and low levels of markers such as CD21 and CD27 (41, 42). These changes show that the cells are

not working normally and may be constantly exposed to the virus (43, 44).

3.5.2. Dysfunction in CHB

In people with CHB, AtM B cells do not function well. They have weak B cell receptor (BCR) signaling and produce fewer antibodies. They also respond poorly to cytokines, which are signals that help immune cells communicate [45, 46]. Even when the virus seems under control, these cells can still be found, suggesting they may help keep inflammation going and contribute to long-term disease [47, 48).

AtM B cells may also respond to other viruses or vaccines. This means they are involved in more than just hepatitis B and can influence the overall immune response. Their behavior can affect how the body reacts to vaccines and other infections [49, 50]. As shown in Table 1, AtM B cells and regulatory B cells (Bregs) have different roles and features in chronic HBV infection. AtM B cells are an important part of the immune system in CHB. Their unique features may influence how the disease develops and how effective treatment will be.

TABLE 2. Comparison of AtM B cells and Regulatory B Cells (Bregs) in CHB infection

Feature	AtM B cells	Bregs
Phenotypic Characteristics	High expression of PD-1, low expression of CD21 [51-53].	Express CD19, CD24, and CD38, high secretion of anti-inflammatory cytokines like IL-10 [54].
Functional Role	Impaired ability to produce effective antibodies, dysfunction in response to HBV [55, 56].	Regulate immune responses by secreting IL-10, reduce the activity of other immune cells [37].
Impact on Disease Progression	Weak immune response, contributing to the persistence of the infection [57].	Help maintain immune balance but may hinder effective immune responses against the virus [58].
Response to Treatment	Less responsive to immunotherapies due to high expression of inhibitory receptors	May respond to immunotherapies, but could dampen inflammation without clearing the virus

appears to be a key factor in the persistence of chronic HBV infection. The regulatory functions of B cells, especially via IL-10 production and interactions with T helper cells, play a significant role in the immune evasion strategies utilized by HBV. These insights into the immune regulation of chronic HBV suggest potential avenues for therapeutic intervention, particularly by targeting Bregs to modulate the immune response and enhance antiviral efficacy. Further research into the exact mechanisms of B cell dysregulation in chronic HBV is needed to fully understand their role in disease progression and to identify strategies for restoring normal immune function.

4. CONCIUSION

In conclusion, the pathogenesis of Chronic Hepatitis B (CHB) is intricately linked to the dysregulation of B cell function, with both atypical memory B cells (AtM B cells) and regulatory B cells (Bregs) playing pivotal roles in sustaining viral persistence and immune dysfunction. While current antiviral therapies have made strides in controlling the virus, they fall short in addressing the underlying immune dysregulation, particularly the dysfunctional B cell response. This underscores the need for novel therapeutic approaches aimed at restoring B cell functionality, focusing on inhibiting the immune-suppressive roles of AtM B cells and Bregs. Future research should focus on better understanding the molecular mechanisms driving these B cell abnormalities and their interactions within the broader immune network. Such efforts will be crucial in developing strategies that not only target the virus more effectively but also promote immune system restoration, paving the way for a more durable and functional cure for CHB.

5. Recommendations for Future Research:

1. Clinical Trials for B Cell–Targeted Therapies: Future studies should test therapies that target B cell dysfunction in CHB. Clinical trials could explore whether modifying the activity of AtM B cells or Bregs can help restore immune balance and control HBV replication.

2. Study B Cell Function Over Time: Long-term (longitudinal) studies should follow patients from acute to chronic HBV infection. This could identify when B cell dysfunction begins and the best time for intervention.

3. Focus on PD-1 and FCRL5 Pathways: More research is needed on the molecular pathways that cause the build-up of AtM B cells. Studying PD-1 and FCRL5 signaling might help in designing drugs that fix or reverse this dysfunction.

4. Improve Vaccine Responses in CHB Patients: Since Bregs may suppress vaccine responses, studies should explore how reducing Breg activity could make the HBV vaccine more effective—especially for people with chronic infection.

Therapeutic Implications

- **Targeting AtM B Cells:** Blocking inhibitory receptors such as PD-1 or FCRL5 may help reactivate functional antibody responses and improve viral clearance.

- **Using TLR Agonists:** Stimulating Toll-like receptors (TLRs) might help overcome immune exhaustion and boost antiviral immunity.
- **Modulating Bregs:** Therapies that reduce IL-10–producing Bregs could improve both natural immune responses and vaccine effectiveness in CHB patients.

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Arabic Abstract

يُعد التهاب الكبد المزمن (CHB) من التحديات الصحية العالمية الكبيرة، على الرغم من توافر اللقاحات والعلاجات المضادة للفيروسات. تشير البيانات المتعلقة بعوامل الإصابة ومعدلات الوفيات إلى أن التهاب الكبد الفيروسي يشكل العامل الرئيس في تفشي هذا المرض. وتُعزى قدرة الفيروس على البقاء والتطور إلى حالة مزمنة إلى قدرته على الاستمرار في البقاء نشطًا أو شبه نشط داخل خلايا الكبد، نتيجة لمقاومته للمادة الوراثية التي تمكنه من التهرب من العلاجات المتوفرة حاليًا. في ظل هذه التحديات، بدأت الأبحاث في البحث عن طرق علاجية بديلة تستهدف الفيروس من داخل جسم العائل. لقد تم التعرف على دور خلايا "ب" في مكافحة العدوى من خلال توليد الأجسام المضادة ضدHBcAg ، حيث يُعتبر التخلص من هذه الأجسام المضادة مؤشراً على فعالية العلاج. ومع ذلك، أظهرت الدراسات وجود خلايا الذاكرة غير النمطية (AtM B cells) التي تحمل مستقبلات مثبطة مثلPD-1 ، وهو ما يساهم في خلل في وظيفة جهاز المناعة، مما يقلل من فعالية الدفاعات المناعية ضد الفيروس ويستمر في الحفاظ على وجوده داخل الجسم. بالإضافة إلى ذلك، على الرغم من أن التأثير الدقيق للخلايا التنظيمية ب (Bregs) على فيروس التهاب الكبد B لا يزال غير واضح بشكل كامل، إلا أن دورها في تعديل الاستجابات المناعية من خلال إشارات مستقبلات التدفق الشبيه بالنوكليوتيد (TLR) بدأ يلقى اهتمامًا متزايدًا.

تهدف هذه الدراسة إلى استكشاف التحولات الفينوتيبية والوظيفية التي تطرأ على خلايا "ب" في سياق التهاب الكبد المزمنB ، مع تسليط الضوء على الفجوات المعرفية في هذا المجال واقتراح استراتيجيات علاجية مستقبلية. إلى جانب تعزيز الفهم حول ديناميكيات خلايا "ب" في العدوى بفيروس التهاب الكبدB ، تسعى هذه الدراسة إلى استكشاف أساليب مبتكرة للوصول إلى علاج وظيفي من خلال فحص التغيرات الفينوتيبية وتأثيراتها على تقدم المرض وفعالية العلاج.