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REVIEW ARTICLE
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DECODING HEPATITIS B VIRUS: MOLECULAR INSIGHTS INTO VIRAL ARCHITECTURE, ENTRY PATHWAYS AND HOST DISEASE DYNAMICS.

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ABSTRACT:

Background: Hepatitis B virus remains a significant global health concern, particularly in endemic regions such as Asia and Africa. Despite the availability of effective vaccines and antiviral therapies, chronic HBV infection continues to cause substantial morbidity and mortality through liver cirrhosis and hepatocellular carcinoma.

Aim: This review aims to provide a comprehensive understanding of the molecular architecture of HBV, its mechanisms of host entry, viral replication, and the progression to chronic liver disease. By decoding these processes, the study highlights potential avenues for improved therapeutic strategies.

Methods: A detailed literature-based analysis was conducted using peer-reviewed articles, molecular virology reports, and clinical studies focusing on HBV structure, genome organization, protein function, viral entry pathways, and the dynamics of host-pathogen interactions. The review integrates molecular data with clinical outcomes to elucidate how viral and host factors shape disease progression.

Key Findings: HBV has a compact, partially double-stranded DNA genome encoding four overlapping open reading frames, each critical for replication and immune evasion. Entry into hepatocytes is mediated by the NTCP, with subsequent formation of cccDNA serving as the key template for viral persistence.

Conclusion: Understanding the molecular and cellular mechanisms underpinning HBV infection is essential for developing more effective antiviral strategies. While current therapies can suppress viral replication, they do not eliminate cccDNA or fully reverse immune dysfunction in chronic carriers. Comprehensive insights into the viral life cycle and host responses provide a foundation for future therapeutic innovations.

Keywords: Hepatitis B virus (HBV), Viral genome organization, HBV surface and core antigens, NTCP receptor-mediated entry, Covalently closed circular DNA (cccDNA), HBV replication cycle,

Host-virus interactions, Chronic hepatitis B progression, Hepatic fibrosis and cirrhosis, HBV-induced hepatocellular carcinoma (HCC).

1.Introduction:

Hepatitis B remains one of the most severe infectious illnesses, responsible for a broad range of liver conditions, including acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. It is estimated that more than one-third of the global population has encountered the hepatitis B virus (HBV), contributing to approximately 257 million chronic infections and around 887,000 deaths annually, mainly due to liver failure and liver cancer (1). A key obstacle in achieving complete viral clearance is the limited understanding of certain aspects of the HBV life cycle. One of the main challenges in treating HBV is the virus's ability to maintain its genetic material in liver cells as a stable form known as covalently closed circular DNA (cccDNA), which acts like a minichromosome (2).

2. Structure of Hepatitis B virus:

HBV is a member of the Hepadnaviridae family and is characterized by its small, 3.2-kilobase DNA genome, which encodes a limited number of proteins. The infectious viral particles, known as Dane particles and measuring approximately 42 nanometers in diameter, are composed of an outer lipid envelope containing three forms of hepatitis B surface antigens—large (L-HBs), middle (M-HBs), and small (S-HBs). This envelope encloses a nucleocapsid, which contains the hepatitis B core protein (HBc), the viral polymerase enzyme (Pol), and the viral DNA genome. (3).

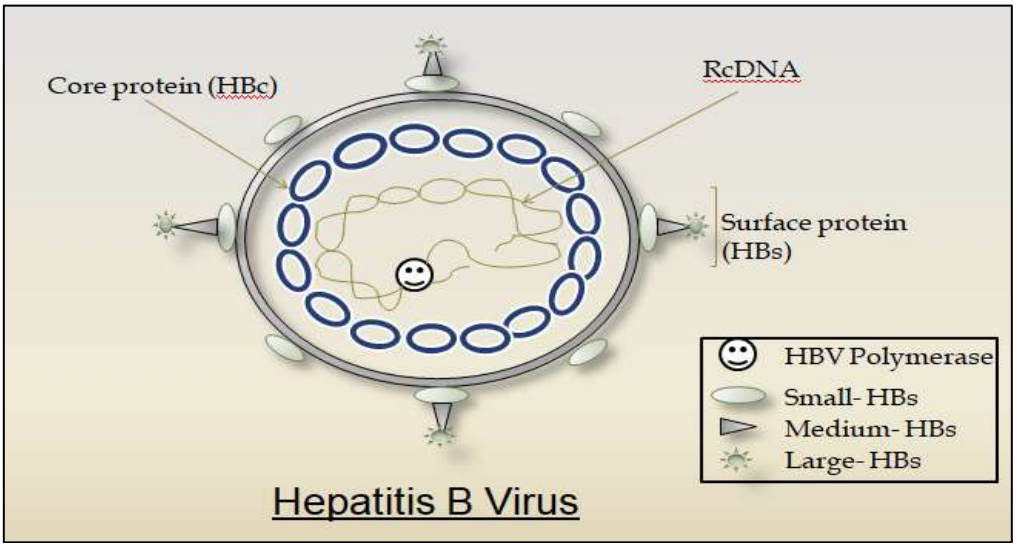

Figure no 1: Structure of HBV particles. Infectious HBV virion (Dane particle) (upper) and non-infectious HBV particles, including enveloped capsids containing immature DNA/RNA, subviral particles (sphere and filament), and naked nucleocapsids (lower).

2.1 Open Reading frames (ORF's):

The hepatitis B virus (HBV) genome consists of four partially overlapping open reading frames (ORFs): ORF P (polymerase), ORF S (surface proteins), ORF C (core protein), and ORF X (HBx protein). These ORFs are responsible for encoding the virus's four primary gene products (Table 1).

Open Reading frames (ORF's)	Production of proteins
1. ORF P (POLYMERASE)	• Polymerase enzyme
2. ORF S (SURFACE)	• large surface antigen (L-HBs) • Middle surface antigen (M-HBs) • Middle surface antigen (S-HBs)
3. ORF C (CORE)	• Hepatitis b virus core antigen (HBcAg) • Hepatitis b virus e antigen (HBeAg) • 22-kDa precore protein (p22cr)
4. ORF x (HBX)	• HBV X protein

Table no. 1: Four overlapping open reading frames in viral genome.

1. **ORF P (VIRAL POLYMERASE)**: It comprises for viral polymerase enzyme, which is involved in viral replication and packaging (4).
2. **ORF S (SURFACE):** It comprises for three HBV surface polypeptides, namely the small (S), medium (M), and large (L) surface antigens that are incorporated in the viral envelope and mediate viral entry (5) (Table no.1).
3. **ORF C (CORE)**, It comprises the viral capsid (essential for viral replication and genome packaging) and several core-related proteins, 22-kDa precore protein (p22cr), including the secreted HBV e antigen (HBe) and a pre-core protein (6).
4. **ORF x (HBX):** It comprises the X protein (HBx), which has been shown to have pleiotropic functions, such as the regulation of viral genome transcription. (7).

3. Entry of Virus:

3.1 Entry of HBV into cytoplasm of cell:

3.1.1 Heparan Sulfate Proteoglycans receptor (HSPGs) (Low affinity binding):

Heparan sulfate proteoglycans (HSPGs) are large biomolecules made up of a core protein linked covalently to multiple heparan sulfate (HS) glycosaminoglycan chains (8). The surface proteins of HBV contain positively charged amino acids—specifically arginine at position 122 and lysine at position 141—within the antigenic loop of the S domain, which is shared by all envelope proteins of the virus. This charge-based interaction facilitates electrostatic binding between HBV and its host cell receptors (9).

3.1.2. Sodium Taurocholate co-transporting Polypeptide (NTCP) Receptor High affinity binding:

The sodium taurocholate co-transporting polypeptide (NTCP), encoded by the SLC10A1 gene located on chromosome 14q24 in humans, functions primarily in the liver (10). It facilitates the co-transport of one bile acid molecule along with two sodium ions (Na^+) into hepatocytes. This sodium-dependent uptake process is electrogenic, as shown by electrophysiological studies that detect transport-related currents, and the stoichiometric ratio between sodium ions and bile acids is approximately 2:1. A key event in the infection process of both hepatitis B virus (HBV) and hepatitis D virus (HDV) is the binding of the preS1 domain of HBV s large surface protein (L protein) to NTCP. Once this attachment occurs, HBV likely enters the cell via endocytosis, and its viral DNA is transported to the nucleus, where infection begins (11).

This entry of HBV is mediated by two types of endocytosis processes:
A. Clathrin-Mediated Endocytosis (CME)
B. Caveolin-mediated endocytosis (CvME)

3.2 Entry of HBV into Nucleus of hepatocyte from cytoplasm:

3.2.1 Nuclear Import of rcDNA:

The transport of relaxed circular DNA (rcDNA) from the cytoplasm to the nucleus is thought to require either a structural rearrangement or partial uncoating of the viral capsid. This process exposes nuclear localization signals (NLS) on the capsid's exterior, enabling interaction with karyopherin α and β. These interactions facilitate the targeting of the nucleocapsid to the nuclear pore complex (NPC) (12).

- **Karyopherin α and β:**

Karyopherin α and β, also referred to as importin α and β, are cellular nuclear transport receptors that play a key role in importing the HBV nucleocapsid into the nucleus. The core protein of HBV (HBc) contains nuclear localization signal (NLS) sequences that are specifically recognized by karyopherin α. Karyopherin β then associates with karyopherin α to mediate the translocation of the nucleocapsid through the nuclear pore complex (NPC) **(**13**).**

- **Nuclear Pore Complex (NPC): Gateway to the Nucleus**

The nuclear pore complex (NPC) serves as the gateway for the entry of the HBV nucleocapsid, which carries relaxed circular DNA (rcDNA), into the nucleus. This structure permits the nuclear import of large molecular assemblies, such as viral capsids, particularly when they are linked to the host's nuclear transport proteins, like karyopherins. Upon interacting with the NPC, the HBV nucleocapsid facilitates the release of rcDNA into the nucleoplasm (14).

- **Nuclear Localization Signals (NLS): Directing Traffic**

The HBV core protein contains distinct amino acid sequences known as nuclear localization signals (NLS), which are specifically recognized by karyopherin α. These signals are crucial for directing the nucleocapsid toward the nuclear import pathway. In the absence of functional NLS motifs, the transport of rcDNA into the nucleus is significantly reduced, thereby hindering the formation of covalently closed circular DNA (cccDNA) (14).

- **Casein Kinase 2 (CK2): Post-Translational Modifications**

Casein kinase 2 (CK2) is a serine/threonine-specific protein kinase that phosphorylates the hepatitis B virus (HBV) core protein. This modification plays a key role in regulating capsid disassembly at the nuclear pore complex, thereby promoting the release of relaxed circular DNA (rcDNA) into the nucleus. CK2 may also modulate the interaction between the core protein and the host's nuclear import machinery. In the absence of CK2 activity, proper uncoating of the core particle may be disrupted, which can block rcDNA release and impair the formation of covalently closed circular DNA (cccDNA). (15).

4.0 Formation of cccDNA from rcDNA:

S. No.	Steps involved in formation of cccDNA	Enzymes/ Factors	Function
1.	Polymerase removal	TDP2 (Tyrosyl-DNA phosphodiesterase 2)	Removes viral polymerase from (-) strand
2.	RNA primer removal	Possibly RNase H-like enzymes	Cleaves RNA primer from (+) strand
3.	DNA synthesis	DNA polymerase κ, η, or δ	Completes (+) strand synthesis
4.	DNA ligation	DNA ligase I, III	Seals nicks to close DNA circle
5.	Chromatinization	Histones (H2A, H2B, H3, H4), Chromatin remodeling complexes	Formation of cccDNA minichromosome

Table no.2: Steps involved in the formation of cccDNA.

The transformation of relaxed circular DNA (rcDNA) into covalently closed circular DNA (cccDNA) is a complex, multi-step process that engages the host cell's DNA damage response pathways, particularly the ATR-CHK1 signaling cascade, along with DNA repair mechanisms and chromatin assembly. Key steps in this process include the removal of the covalently attached viral polymerase from the negative strand and the RNA primer from the positive strand of rcDNA, trimming of the terminal redundancy on the negative strand, completion of the positive DNA strand, and the final ligation of both strands to form a stable cccDNA molecule.(16,17,18). Detaching the viral polymerase from rcDNA is regarded as an essential step in the formation of cccDNA. This process results in the generation of deproteinated (DP) or protein-free rcDNA, which is believed to serve as an intermediate in the synthesis of cccDNA. (19, 20). The DNA repair enzyme tyrosyl-DNA phosphodiesterase 2 (TDP2) has been demonstrated in vitro to cleave the bond between the viral polymerase and the relaxed circular DNA (rcDNA) of both hepatitis B virus (HBV) and duck hepatitis B virus (DHBV). (21, 22) (Table no.2). Nevertheless, human HBV infection can still occur in TDP2-deficient cells, suggesting that other proteins with similar functions may compensate for the absence of TDP2 in facilitating this process (23). Alternatively, the host enzyme flap endonuclease 1 (FEN1) has been implicated in the formation of cccDNA. It is thought to recognize and cleave a 5' flap-like structure on the negative strand of rcDNA, thereby removing both the terminal redundancy (r sequence) and the attached viral polymerase. (24) (Figure no.2).

DNA polymerase κ (kappa) is a translesion synthesis enzyme known for its ability to bypass damaged DNA, albeit with low fidelity. It plays a role in filling the gaps present in the incomplete strands of rcDNA. Another translesion polymerase, DNA polymerase η (eta), is particularly efficient at bypassing UV-induced thymine dimers and has been implicated in the repair of the positive strand gaps in rcDNA. Some studies suggest that polymerase η is necessary for optimal cccDNA formation in liver cells. DNA polymerase δ (delta), a high-fidelity enzyme involved in lagging strand synthesis and general DNA repair, also contributes to the accurate repair and ligation steps required for complete cccDNA synthesis. In addition, it supports strand displacement and repair in cooperation with replication cofactors such as proliferating cell nuclear antigen (PCNA) and replication factor C (RFC) (Figure no.2**)** (25).

Topoisomerases I (TOP1) and II (TOP2) have been identified as essential for both the initial generation and intracellular amplification of HBV cccDNA. Their involvement is likely linked to the circularization process, with TOP1 acting on the negative strand and TOP2 potentially facilitating the circularization of both strands of the relaxed circular DNA (rcDNA) (26).

DNA ligases 1 and 3 are involved in sealing both DNA strands during the conversion of rcDNA into cccDNA (27). The presence of an intermediate form, known as closed minus-strand rcDNA (cM-rcDNA), in HBV-replicating cells suggests that the ligation process may vary depending on the DNA strand involved and could be specific to certain ligases. Supporting this, a recent study using both yeast and human cell extracts identified five key components of the lagging strand synthesis machinery necessary for cccDNA formation: proliferating cell nuclear antigen (PCNA), replication factor C (RFC) complex, DNA polymerase δ, flap endonuclease 1 (FEN1), and DNA ligase 1. These findings reinforce observations from several previous investigations (see Figure 2) (28).

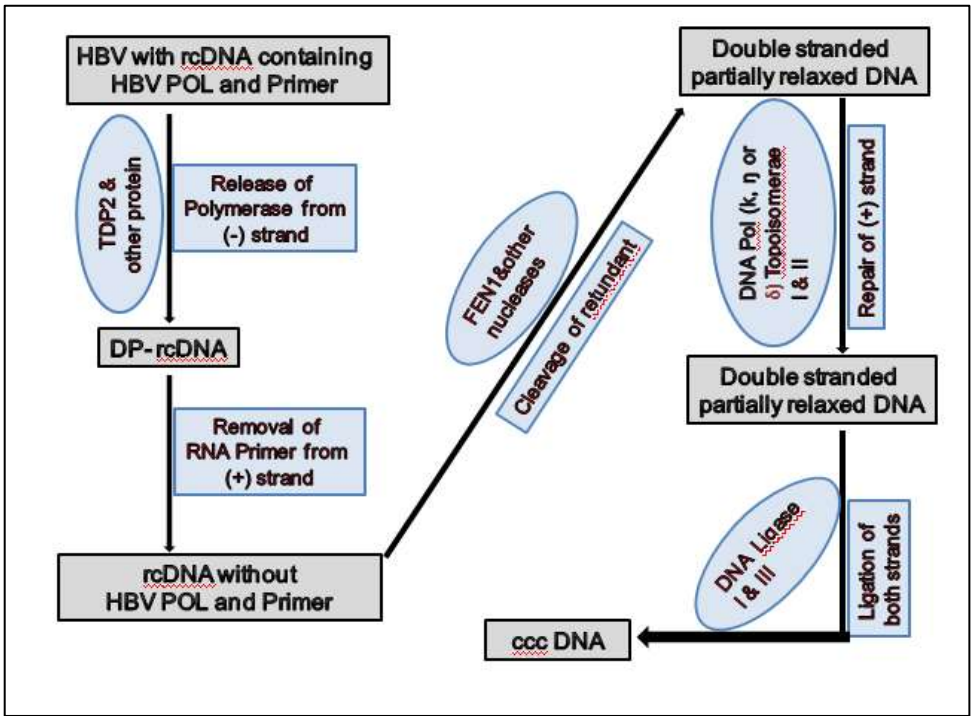

Figure no.2: Various factors and enzymes involved in the formation of cccDNA from rcDNA.

5.0 Different stages of progression of disease in hepatitis B virus infection:

5.1 Acute HBV infection:

Acute hepatitis B is a short-duration liver infection that develops within the first six months following exposure to the hepatitis B virus (HBV). This early stage of HBV infection can vary in presentation, ranging from no noticeable symptoms to more severe manifestations such as jaundice, fatigue, and liver inflammation. HBV is primarily transmitted through contact with infected blood and bodily fluids. Common transmission routes include unprotected sexual activity, sharing of needles or syringes, mother-to-child transmission during birth, and unsafe practices involving tattoos or body piercings. The virus typically has an incubation period of approximately 60 to 90 days, which is the time between exposure and the onset of symptoms (29).

5.2 Chronic HBV infection:

Chronic hepatitis B refers to a long-term liver condition defined by the persistence of hepatitis B surface antigen (HBsAg) in the blood for more than six months. While some individuals with chronic infection remain in an inactive state with minimal health impact, others may experience disease progression leading to liver fibrosis, cirrhosis, or even hepatocellular carcinoma (HCC) (30).

Different stages of the chronic hepatitis B are
A. Immune Tolerant Phase
B. Immune Active Phase
C. Inactive Carrier Phase
D. HBeAg-Negative Reactivation Phase

5.3 Liver Fibrosis:

The natural course of hepatitis B virus (HBV) infection is complex and primarily affects the liver, where interactions between viral components and the host immune response trigger cycles of hepatocyte injury and subsequent tissue repair (31). This ongoing repair process results in the accumulation of extracellular matrix, which gradually leads to liver fibrosis. The HBV X protein is believed to contribute directly to both fibrotic and cancer-promoting processes within the liver (32). The rate at which fibrosis progresses can vary—some individuals may experience rapid deterioration, while others may progress slowly or unpredictably, depending on the extent of liver

inflammation and cellular damage. Accurate evaluation of liver fibrosis is essential for determining disease prognosis, guiding treatment urgency, and monitoring therapeutic response. Notably, the initial severity of liver disease is a key indicator of long-term outcomes, and advanced fibrosis identified through noninvasive testing is a strong, independent risk factor for the development of hepatocellular carcinoma (HCC) (33).

5.4 Liver Cirrhosis:

5.4.1 Progression to cirrhosis:

The incidence of cirrhosis is higher in patients with HBeAg-positive chronic hepatitis B compared to those with HBeAg-negative chronic hepatitis, particularly in individuals experiencing the HBeAg-negative reactivation phase, also referred to as the "Immune Escape Phase" of chronic hepatitis B (34). Several factors contribute to an increased risk of cirrhosis progression, including active viral replication, advanced age, significant fibrosis on liver biopsy, alcohol consumption, co-infection with other hepatitis viruses (C or D), co-infection with HIV, and potentially the HBV genotype (35,36).

5.4.2 Compensated and Decompensated cirrhosis:

Compensated cirrhosis is an early stage of liver cirrhosis characterized by significant scarring of the liver, yet it remains capable of performing most of its critical functions. At this stage, there are typically no noticeable symptoms or complications. In contrast, decompensated cirrhosis represents the advanced phase, where the liver loses its ability to carry out essential functions, leading to severe complications such as portal hypertension and liver failure. Approximately 20% of individuals with compensated HBV cirrhosis will progress to decompensation within five years. The five-year survival rates for patients with compensated HBV cirrhosis are estimated to be 72% for those who are HBeAg-positive and 97% for those who are HBeAg-negative (37).

5.5 Hepatocellular Carcinoma (HCC):

Hepatocellular carcinoma (HCC) is a primary liver cancer that often arises in individuals with chronic Hepatitis B virus (HBV) infection, regardless of whether cirrhosis is present. While various factors can contribute to liver cancer, HBV has the ability to directly induce HCC even in the absence of cirrhosis, making HBV-associated HCC particularly unique and hazardous. The development of HCC involves both HBV and host-related factors. Males and older individuals are at an increased risk for HCC. Additional risk factors include environmental exposures such as smoking, alcohol consumption, aflatoxin B1, and co-infection with Hepatitis C virus (HCV) (38, 39).

5.6 End-Stage Liver Disease / Liver Failure

End-Stage Liver Disease (ESLD) represents the final phase of ongoing liver damage, where the liver loses its ability to perform vital functions such as metabolism, synthesis, and detoxification due to irreversible scarring (cirrhosis). This condition encompasses several clinical forms, including acute-on-chronic liver failure (ACLF), acute decompensation of cirrhosis (ADC), chronic liver failure (CLF), and decompensated hepatocellular carcinoma. Infections are among the most common complications in patients with ESLD, often triggering severe inflammation, dysfunction or failure of extrahepatic organs, and a significant increase in mortality (40, 41).

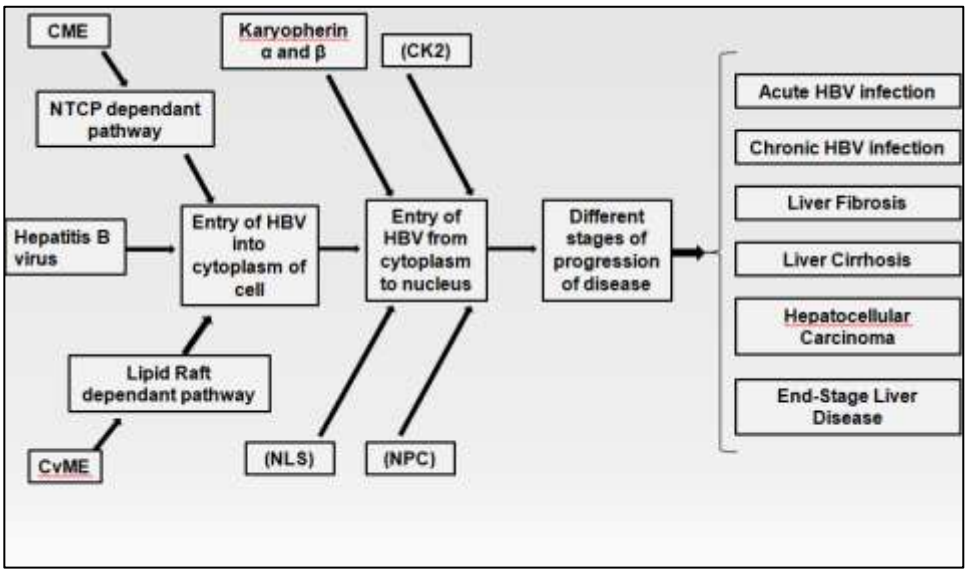

Figure no.3: Shows the complete life cycle of HBV from the entry to progression of disease. CME(Clathrin-Mediated Endocytosis), CvME(Caveolin-mediated endocytosis, NTCP(Sodium Taurocholate co-transporting Polypeptide Receptor), NLS(Nuclear Localization Signals), NPC(Nuclear Pore Complex), CK2(Casein Kinase 2).

Future Considerations: Future research should prioritize the development of cccDNA-targeted therapies, immune modulators that restore antiviral immunity, and entry inhibitors that prevent initial hepatocyte infection. Additionally, studies exploring viral-host epigenetic interactions and HBV-induced oncogenesis may uncover novel targets for long-term disease control and potential cure. Integration of molecular diagnostics with personalized therapy holds promise for advancing the clinical management of chronic hepatitis B.

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9.0 Author Biography

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