Mechanism of Hepatitis B Virus Persistence in Hepatocytes and Its Carcinogenic Potential

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Liver disease associated with persistent infection with hepatitis B virus (HBV) continues to be a major health problem of global impact. Despite the existence of an effective vaccine, at least 240 million people are chronically infected worldwide, and are at risk of developing liver cirrhosis and hepatocellular carcinoma. Although chronic HBV infection is considered the main risk factor for liver cancer development, the molecular mechanisms determining persistence of infection and long-term pathogenesis are not fully elucidated but appear to be multifactorial. Current therapeutic regimens based on the use of polymerase inhibitors can efficiently suppress viral replication but are unable to eradicate the infection. This is due both to the persistence of the HBV genome, which forms a stable minichromosome, the covalently closed circular DNA (cccDNA), in the nucleus of infected hepatocytes, as well as to the inability of the immune system to efficiently counteract chronic HBV infection. In this regard, the unique replication strategies adopted by HBV and viral protein production also appear to contribute to infection persistence by limiting the effectiveness of innate responses. The availability of improved experimental systems and molecular techniques have started to provide new information about the complex network of interactions that HBV establishes within the hepatocyte and that may contribute to disease progression and tumor development. Thus, this review will mostly focus on events involving the hepatocyte: the only target cell where HBV infection and replication take place.

Keywords. hepatitis B; DNA; molecular techniques.

Characteristic of hepatitis B virus (HBV) is its high tissue and species specificity, as well as a unique genomic organization and replication mechanism. Indeed, humans are the only natural hosts of HBV infection, and the hepatocyte is the only target cell that is susceptible for infection and where viral replication takes place. Moreover, in HBV, unlike in hepatitis C virus (HCV), hepatocellular carcinoma (HCC) may develop not only in cirrhotic, but also in noncirrhotic livers due to mechanisms that can be present even in livers with minimal fibrosis.

HBV Structure
The infectious virion consists of a spherical lipid envelope that contains a nucleocapsid formed by the core protein (HBcAg). Within the nucleocapsid, the viral genome forms a relaxed circular partially double-stranded DNA (rcDNA) of only approximately 3200 bp, which is covalently linked to the viral polymerase. The HBV genome is organized in a highly condensed way, where all genes are encoded within open reading frames that largely overlap. The viral membrane is formed by host-derived lipids and 3 envelope proteins that are named, according to their size, preS1 (or large), preS2 (or middle), and S (or small). All 3 proteins share the same C-terminal domain, which contains the surface antigen (HBsAg), while the preS2 and preS1 proteins display progressive N-terminal extensions and are essential for receptor recognition [1]. Notably, 3 types of viral particles can be visualized in the infectious serum by electron microscopy: the infectious virions and the subviral particles (SVPs), which are present as filaments or spheres and are exclusively composed of envelope proteins and lipids [2]. The biological function of these noninfectious SVPs, which are produced in larger amounts compared to the virions, is not fully understood, but it has been suggested that they may both absorb the neutralizing antibodies produced by the host and also directly contribute to the impairment of immune responses [3].

The Infection Process
HBV is a blood-borne pathogen transmitted by percutaneous exposure to infected blood or body fluids. Through the bloodstream, the virus reaches its target organ: the liver. Accumulating evidence from in vitro and in vivo experimental studies indicates that the infection process is accompanied by unconventional slow kinetics of infection and spreading [1]. However, because of the limited availability of robust infection systems, knowledge of the molecular events occurring in the early phases of infection is still scant, but it certainly involves interactions with multiple host factors.

In HBV infection, the cell entry process involves first a noncell-type specific primary attachment to the cell-associated heparan sulfate proteoglycans [4], which is followed by an irreversible binding of the virion to a hepatocyte-specific receptor.
Both myristoylation and integrity of the first 77 amino acids of the preS1 domain of the large envelope protein are known to be essential for infectivity [5]. Notably, the entry of both HBV and hepatitis delta virus, which also needs the HBV envelope for infection and propagation, was shown to be blocked by a small myristoylated lipopeptide derived from the preS1 domain of the large envelope protein [6–8]. Although the differentiation status and the polarization of the hepatocytes were shown to play an essential role in the viral entry process [9], it was only in 2012 that Yan and coworkers could identify the Na+-taurocholate cotransporting polypeptide (NTCP) as the functional cellular receptor permitting hepatitis B and delta viruses to enter the hepatocyte [10]. This study demonstrated very elegantly that the binding of the virion to the transmembrane transporter NTCP is mediated by the preS1 domain of the HBV envelope protein. NTCP is known to mediate most of the hepatocellular Na+-dependent uptake of bile salts [11] and is exclusively expressed on the basolateral membrane of highly differentiated primary hepatocytes, thus explaining the strict liver tropism of HBV.

The steps that follow viral entry are still poorly characterized. Experimental evidence indicated that HBV enters the hepatocyte via endocytosis [12] before the nucleocapsids are transported via microtubules to the nuclear periphery, where they were shown to interact with the nuclear pore complexes [13]. Here, the mature capsids disintegrate, permitting the release into the nucleoplasm of both core proteins and viral genome. Recent experiments showed that HBV uses cellular DNA repair enzymes, such as the tyrosyl-DNA-phosphodiesterase (TDP) 1 or TDP2, to remove the viral polymerase and hence to initiate covalently closed circular DNA (cccDNA) biogenesis [14]. Thus, establishment of productive HBV infection requires (1) the removal of the covalently linked viral polymerase; (2) completion of the positive DNA strand; and (3) ligation of the viral genome, to form a circular, double-stranded, covalently closed “plasmid-like” cccDNA molecule, which then associates with histone and nonhistone proteins to build a minichromosome [15] within the hepatocyte nucleus.

The cccDNA minichromosome utilizes the cellular transcriptional machinery to produce all viral RNAs necessary for protein production and viral replication, which takes place in the cytoplasm after reverse transcription of an over-length pregenomic RNA (pgRNA). Similar to cellular chromatin, viral transcription is regulated by the activity and dynamic interplay of numerous transcription factors, coactivators, corepressors, and chromatin modifying enzymes [15]. While the pgRNA provides all components required for the production of new HBV DNA–containing nucleocapsids, the production of the envelope proteins, which are needed for virion secretion and SVP production, depends on the transcription of the so-called subgenomic HBV RNAs (preS/S). Although a number of liver-specific transcription factors involved in cccDNA transcription have been identified, knowledge of the molecular mechanisms regulating HBV transcription in infected cells is still limited [15]. Both subgenomic and pregenomic RNA is transported into the cytoplasm, where it is respectively translated or used as the template for progeny genome production. The binding of polymerase to the pgRNA, in concert with the core proteins, initiates the packaging process. Within the nucleocapsids and protected from intracellular innate immune mechanisms, the reverse transcription takes place. In brief, the first product is a single-stranded DNA of minus polarity that remains covalently linked to the polymerase. The pgRNA is concomitantly degraded, except for a few nucleotides that serve as primer for plus-strand DNA synthesis [16]. Notably, infection studies performed in ducks and woodchucks revealed that, in the early phases of infection, the newly synthesized nucleocapsids can be transported into the cell nucleus to build a cccDNA pool [16]. Thus, intracellular cccDNA amplification was shown to play a fundamental role for the establishment of a cccDNA pool in duck and woodchuck hepatocytes, where a high copy number of cccDNA molecules is generally detected (up to 50 molecules/cell). In contrast, lower cccDNA intrahepatic loads are more frequently determined in human liver biopsies obtained from chronically HBV-infected patients [17–19] and in chronically HBV-infected human-liver chimeric mice (median, 0.5–5 copies/cell) [7, 20, 21], suggesting that different viral and host mechanisms may control cccDNA dynamics and cccDNA pool size in human infected hepatocytes. In this regard, a sophisticated experimental study provided evidence that HBV converts the rcDNA into cccDNA less efficiently than duck hepatitis B virus (DHBV) in the same human cell background [22].

The final replication step, the assembly and release of rcDNA containing nucleocapsids, is also not fully elucidated, but recent studies indicated that the release of infectious viral particles occurs via multivesicular bodies, whereas the release of SVPs appears to proceed via the general secretory pathway [23].

In sum, it seems that in the process of infection establishment, HBV has developed sophisticated strategies that (1) enable the virus to camouflage its genome by building a minichromosome that strongly resembles the host chromatin, and (2) permit the production of new viral progeny without offering many possibilities to the host defense mechanisms to recognize the infection.

**FACTORS CONTRIBUTING TO MAINTENANCE OF HBV INFECTION**

HBV infection in immunocompetent adults generally results in a self-limited, transient liver disease, where viral control is achieved in >95% of adults. On the other hand, >90% of individuals exposed to HBV at birth or in perinatal age become persistently infected [24]. Experimental studies indicated that not only the age at infection, but also the route and the size of the inoculum influence the kinetics of viral spread and so may affect immunological priming and infection outcome [25]. In general, resolution of infection typically requires effective viral recognition.
and concerted induction of innate and adaptive immune responses. Animal and clinical studies have demonstrated that in acute self-limited HBV infection, the CD8+ and CD4+ T-cell responses to HBV proteins are strong, polyclonal, and multispecific [26], whereas in chronic HBV infection immune responses appear weak and narrowly focused [27]. Moreover, studies in chimpanzees [28] and patient observations [29] showed that HBV does not induce a strong activation of the innate immune system and of interferon-stimulated genes (ISGs) in the early phases of infection. Thus, while viral replication is initiated through the establishment of a cccDNA minichromosome without stimulating antiviral mechanisms of the hepatocyte, the slow kinetics of intrahepatic viral spread as well as the production of specific viral components (see below) may also contribute to the limited effectiveness of the host antiviral response [24].

**Stability of cccDNA**

The use of highly selective real-time polymerase chain reaction assays permits cccDNA quantification both in experimental systems and in human liver biopsies, thus enabling investigation of the impact of antiviral therapy on cccDNA loads. A significant decrease in cccDNA levels (approximately 1-log reduction) is generally achieved after 1 year of therapy [19, 30–34]. Such reduction is presumed to derive from the lack of incoming viruses from the blood and insufficient recycling of viral nucleocapsids to the nucleus, due to the strong inhibition of viral DNA synthesis in the cytoplasm. Nevertheless, long-term antiviral therapy is needed to achieve significant reduction of the cccDNA pool [19, 32, 34, 35]. This is not surprising, as polymerase inhibitors target neither the cccDNA directly, nor its transcriptional activity [24, 36]. Thus, despite the absence of detectable viremia, cccDNA persistence within hepatocytes is the reason for the failure of viral clearance and relapse of viral activity after antiviral treatment with polymerase inhibitors in chronically infected individuals.

A stronger cccDNA reduction (2-log) was determined in patients who had received 1 year of combination therapy with polymerase inhibitor and interferon alpha (IFN-α) [32, 35], which has been shown to have both immunomodulatory and direct antiviral effects. In this regard, studies in HBV-transgenic mice have reported the capacity of IFN-α to accelerate pgRNA degradation and core particle decay [37–40]. Furthermore, experiments performed in vitro and in HBV-infected humanized mice revealed that IFN-α can lower the levels of both pregenomic and subgenomic HBV RNA by inducing epigenetic modifications of the histones bound to the cccDNA minichromosome [41]. Thus, these studies showed that by targeting cccDNA transcription, IFN-α can directly contribute to the decline of viral antigen amounts (HBcAg, HBsAg). Moreover, IFN-α administration was also shown to promote partial cccDNA degradation. In this regard, upregulation of cytidine deaminases mediated by the induction of IFN-α and NFκB pathways was recently shown to promote partial cccDNA degradation [42].

Both in vitro and in vivo studies indicated that the cccDNA minichromosome is very stable in quiescent hepatocytes [43, 44]. However, studies in ducks suggested that a greater cccDNA reduction could be achieved in animals treated with polymerase inhibitors and displaying higher hepatocyte proliferation rates [45]. Significant cccDNA decrease was also determined in woodchuck hepatitis virus (WHV)-infected woodchuck hepatocytes when cell turnover was induced in vitro by addition of cellular growth factors and viral replication was suppressed by the viral polymerase inhibitor adeovir [43]. Furthermore, the identification of uninfected cccDNA-negative cell clones containing “traces” of the infection in the form of viral integration demonstrated that cccDNA clearance without cell destruction can occur in chronically infected livers [46, 47]. Thus, killing of hepatocytes may be instrumental not only to eliminate infected cells but also to induce hepatocyte proliferation, which in turn may favor cccDNA loss [48].

Immune CD8+ T cells and natural killer cells have the capacity not only to destroy the cccDNA together with the infected cell but also to induce proliferation of the remaining hepatocytes to compensate for the cell loss [27]. Thus, during chronic HBV infection, immune-mediated cell injury and compensatory hepatocyte proliferation may accelerate cccDNA decline and selection of cccDNA-free cells. Upon hepatocyte division, the cccDNA molecules may be distributed among daughter cells, leading to the dilution of the nuclear cccDNA pool. Because the cccDNA is not a cellular chromosome equipped with centromeric structures, the cccDNA molecules may become distributed in an unequal way or even get lost during cell mitosis [46, 48]. Previous studies reported that hepatocyte proliferation can lead to a remarkable loss of the intrahepatic cccDNA loads in immunodeficient human liver chimeric mice [48]. Such findings point out the important role that immunomodulating factors may play in reducing cccDNA loads and activity.

**HBV Proteins**

The effectiveness of the immune status is essential to achieve control of the infection. However, the production of specific viral components, as well as the stability of the cccDNA, may contribute to HBV infection persistence by creating a state of immune tolerance. Although in vitro studies indicated that the innate immune response of the hepatocytes may sense the infection [49–51], only modest activation of ISGs was determined in human hepatocytes after in vivo HBV infection in chimeric mice [21, 52]. The lack of production of type I interferons determined both in patients [29] and animal models [53, 54] is thought to contribute to the establishment of HBV persistence. Furthermore, the limited effectiveness of IFN-α treatment observed in a great proportion of individuals chronically infected with HBV may reflect an incapacity of innate immune responses to control the infection.
with HBV [55] strongly suggests that HBV may have evolved strategies to avoid or even suppress the induction of pathways of the antiviral innate immune response. In support of the concept that HBV can sabotage pathways of the IFN response, a study in human-liver chimeric mice showed that administration of regular IFN-α failed to promote induction of several human IFN-regulated genes and detectable nuclear translocation of STAT1 in HBV-infected human hepatocytes, although STAT1 nuclear accumulation and enhancement of the same antiviral defense mechanisms were promptly induced in uninfected animals [21]. Moreover, in vitro studies showed that HBV proteins may counteract the IFN system by inhibiting the methylation of STAT protein, possibly through upregulation of PP2Ac [56], while the HBV polymerase was shown to inhibit the IFN-inducible MyD88 promoter by blocking the nuclear translocation of STAT1 [57]. Furthermore, the viral polymerase was recently shown to play a role in the suppression of IFN-β production by interacting with STING, a stimulator of interferon genes, which has been identified as a central factor in foreign DNA recognition and antiviral innate immunity [58].

It has been suggested that SVPs, which typically outnumber the virions by a factor of 1000- to 10 000-fold, may contribute to the limited effectiveness of the immune responses by promoting the formation of circulating immune complexes, and so by sequestering neutralizing antibodies from circulation [3]. Furthermore, plasma-derived HBsAg was reported to inhibit Toll-like receptor (TLR) 9–mediated IFN-α production by plasmacytoid dendritic cells, probably via stimulation of SOCS-1 expression [59].

Besides the production of large amounts of empty SVPs, HBV produces and secretes a nonparticulate form of the nucleoprotein, the precore protein, or HBeAg, which is not required for viral infection or replication; however, experimental and clinical evidence has indicated that its presence may contribute to viral persistence by exerting important immunomodulating functions [60]. The precore protein is translated from a distinct transcript that also contains the full core gene but encoding a stop codon, may present selective advantages, possibly by limiting the cytotoxic T-lymphocytes (CTL)-mediated clearance of infected hepatocytes [62]. On the other hand, the selection of HBeAg variants is associated with increased viral activity [18], more severe liver disease, and worse prognosis.

The HBV X protein is a nonstructural, multifunctional regulatory protein with transactivating potential, which was shown to interfere also with innate immunity by downregulating mitochondrial antiviral signaling protein by suppressing the RIG-1/MDA5 pathway and by interacting with members of the cellular epigenetic family [63]. Altogether, these studies suggest that distinct virus-mediated mechanisms may contribute to the limited effectiveness of the immune responses in HBV infection and thereby may significantly contribute to viral persistence.

**FACTORS INVOLVED IN DISEASE PROGRESSION AND CARCINOGENESIS**

Hepatocellular carcinoma is the third leading cause of cancer-related death, with >500 000 new cases annually diagnosed worldwide. Epidemiological studies have shown that chronic infection with HBV can cause various degrees of liver damage and is strongly associated with the development of liver cirrhosis and HCC [64–66]. Besides environmental factors, host genetic factors also appear to play a role in HBV-associated liver disease progression. Nevertheless, only a limited number of studies identified genetic loci that are clearly associated with HBV-related liver cirrhosis [67]. On the other hand, viral factors including HBV genotypes, HBV DNA levels, HBeAg status, and the presence of core promoter mutations in the HBV genome, as well as coinfection with other viruses, have been reported to contribute to disease progression. Although HBV does not cause direct cytopathic effects, the oncogenic role of HBV might involve a combination of direct and indirect effects of the virus during the multistep process of liver carcinogenesis. In this regard, hepatocyte proliferation driven by host immune responses is a recognized driving force of liver cell transformation, as these events can favor the accumulation of genetic alterations within the hepatocytes. Indeed, HBV may sensitize the hepatocytes to oncogenic transformation by promoting integrations of the viral genome into host chromosomes, by causing epigenetic changes of the host chromatin [68] and the expression of microRNAs [69], as well as through prolonged expression of viral gene products [67].

The transcriptional regulatory protein HBx is endowed with tumor promoter activity. Numerous DNA transfection experiments have shown that overexpression of HBx causes transactivation of a wide range of viral elements and cellular promoters [70]. Moreover, in vitro studies have shown that HBx can affect various cytoplasmic signal transduction pathways (ie, Src kinase, Ras/Raf/MAP kinase, Jak1/STAT), as well as to control the degradation of cellular and viral proteins [71]. Although the exact role of HBx in the context of HBV infection has not
been fully elucidated, several lines of evidence have convincingly shown that HBx is required for cccDNA-driven HBV replication and to maintain virion productivity [72–74]. These findings are also in agreement with data showing that HBx is recruited to the cccDNA minichromosome, where it appears to be involved in epigenetic control of HBV replication [69, 75]. Interestingly, a study suggested that HBx can act as a potent epigenetic modifying factor in the human liver, by modulating the transcription of DNA methyltransferases that are required for maintenance of hypomethylation of tumor suppressor genes (TSGs) [76].

Unlike the provirus DNA of retroviruses such as human immunodeficiency virus (HIV), HBV does not need to integrate its genome into the host genome as part of its replication life cycle. Nevertheless, integrations of HBV DNA sequences do occur, particularly in the presence of DNA damage [77] and cell turnover, as experimental studies in woodchucks and chimpanzees have documented [46, 47]. By inserting viral genome sequences into the host chromosomes, HBV causes alteration of human genome, such as genomic instability and direct insertional mutagenesis, a process that may play important roles in the initiation of hepatocellular carcinogenesis, as integrations have been associated with changes in genes involved in cell proliferation, differentiation, and survival. Moreover, HBV DNA integrations were shown to occur at early steps of clonal tumor expansion. In addition, DNA methylation was observed in the early stage of cancer development. Whereas genomic hypomethylation can increase chromosome instability, localized hypermethylation can decrease the expression of TSGs, thus increasing the risk of HCC development. Of note, most HBV-related HCCs show the integration of HBV DNA sequences, and analysis of HBV-integrated sequences has revealed that HBx is the most common open reading frame integrated into the host genome [68, 69].

Numerous transcription factors implicated in the activation of hepatic metabolic processes, such as hepatocyte nuclear factor, CREB, retinoid X receptor, and peroxisome proliferator-activated receptors, are known to bind the HBV genome, and the recruitment of liver-enriched transcription factors on the cccDNA minichromosome appears to be essential for controlling viral gene expression [15, 78]. On the other hand, interactions between viral components and cellular factors may also impact the liver metabolism. Recent studies showed that binding of the preS1 domain of the large envelope protein of HBV limits the hepatocellular uptake of bile salts [79, 80] and the expression profile of key genes involved in bile acid metabolism [81]. These findings suggest that in the setting of chronic HBV infection, alterations of the hepatocellular uptake of bile acids may lead to different levels of compensatory metabolic alterations and also promote disease progression. Moreover, mutations in the pre-S/S gene of HBV and, in particular, deletions in pre-S in integrated HBV DNA sequences have been reported in HCC cases compared with chronic or asymptomatic cases. These mutations may impair the secretion of HBsAg, leading to increased endoplasmic reticulum and oxidative stress in hepatocytes. Mutated variants of the envelope proteins have also been shown to interact with cyclin A, a regulator of the cell division cycle [82]. These observations support a role for pre-S mutations in hepatocyte hyperplasia and possibly in the process of HBV-related hepatocarcinogenesis [83]. Moreover, mutations in the core promoter region that are known to cause downregulation of precore messenger RNA and HBeAg production have been associated with fulminant hepatitis, severe liver disease, and an increased risk of HCC [83].

**SCREENING FOR HBV-RELATED HCC**

**Clinically Relevant Risk Factors for HCC in HBV Infection**

Cirrhosis is the single most important clinical risk factor for the development of HCC in patients with chronic hepatitis B. However, as HBV is directly carcinogenic, HCC may arise in a non-cirrhotic liver. This highlights the importance of considering other clinically relevant HCC risk factors in the management of chronic hepatitis B, which can be separated into host and viral factors [84] (summarized in Table 1).

**Current Recommendations for HCC Surveillance**

Guidelines on HCC screening and surveillance have been issued by the European Association for the Study of the Liver (EASL), the Asian Pacific Association for the Study of the Liver (APASL), and the American Association for the Study of Liver Diseases (AASLD) (Table 2) [85–87]. All 3 guidelines recommend HCC surveillance in patients with compensated and decompensated cirrhosis. Although the APASL guidelines acknowledge the occurrence of HCC in the noncirrhotic liver, it calls for further studies to better define the at-risk group [86]. The EASL guidelines also recommend surveillance in HBV carriers with active liver disease.

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<th>Table 1. Clinically Relevant Risk Factors for Hepatocellular Carcinoma in Patients With Chronic Hepatitis B</th>
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Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.
hepatitis and patients with family history of HCC, but it is unclear what constitutes active hepatitis [85]. In clinical practice, we screen these patients for HCC. Recently, in addition to cirrhosis and family history, the AASLD guidelines specifically consider age, sex, and ethnic origin in selecting patients for surveillance [87]. In particular, Africans and North American blacks are recommended for surveillance regardless of their age and disease status. Of note, HCV/HIV-coinfected patients do have a higher risk for the development of advanced liver disease and liver cirrhosis and, hence, the development of HCC. Therefore, coinfected patients should receive regular HCC screening. Based on the risk factors, a number of risk scores have been developed and validated over the last years, unfortunately with inconclusive results. The performance of the HCC risk scores, such as REACH-B, GAG-HCC, and others, appears to be inferior in white patients compared to Asian patients [84]. Therefore, the application of risk scores has not been sufficiently conclusive to be added to regional guidelines.

All 3 guidelines support HCC surveillance every 6 months. APASL recommends using abdominal ultrasonography and serum alpha-fetoprotein (AFP) for surveillance [86]. In contrast, EASL and AASLD recommend abdominal ultrasonography only because of the limited sensitivity and specificity of serum HCC biomarkers [85, 87]. In our daily clinical practice, we are following the EASL guidelines applying surveillance using ultrasonography every 6 months, and additionally we are checking for AFP levels as suggested in the APASL guidelines.

CONCLUSIONS

The availability of improved experimental systems and molecular techniques has begun to provide new insight about the complex network of virus−host interactions that are established in the course of infection. In particular, the identification of the cellular factors that are involved in cccDNA biogenesis and stability shall be further encouraged as such knowledge may be crucial for the development of therapeutic strategies aiming at depleting the intrahepatic cccDNA reservoir. Furthermore, studies demonstrating the possibility of silencing cccDNA activity provide a rationale for the development of treatments aimed at not only reducing HBV replication, but also promoting a significant reduction of viral protein expression, factors that may both slow disease progression and improve the chances of gaining immune control of the infection.

Notes

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