Chronic hepatitis C, attributed to infection with hepatitis C virus (HCV), is a global health problem. The overall prevalence of viral hepatitis worldwide is estimated to be 3–5% with over 175 million people infected with HCV. Clinically, HCV can establish a persistent, chronic infection contributing to progressive liver disease, including cirrhosis and hepatocellular carcinoma (HCC), requiring intensive treatment regimens, possible liver transplantation and long-term care. Due to the chronic nature of HCV infection and the tremendous burden on healthcare resources, clinicians and laboratorians have looked for key epidemiological, pathological and viral characteristics that may provide insight into disease progression, severity and response to therapy to permit the administration of effective therapeutic regimens as well as long-term management of infected individuals. Determination of viral genotype has been identified as one parameter that could provide direction in the clinical management of patients with chronic HCV infections. The following review provides background on determination of HCV genotypes and the relevance of viral genome characterization in the current clinical setting.

Introduction

Molecular characterization of viruses has moved from the research bench to reference laboratories and clinics. Different characteristics of viruses can effect the transmission of disease, viral pathogenesis, response to therapy and the outcome of infection. Clinicians routinely examine molecular information about viruses to administer effective therapeutic interventions and make critical decisions with regards to the management of infected patients. Three general approaches have been employed to characterize viruses and have led to the grouping of viral isolates [1]. The first approach, serotyping, examines the pattern of viral neutralization by antibodies. Another approach, phenotyping, assesses differences in disease patterns, cytopathology or response to antiviral agents when suitable model systems are available. Finally, investigators may look for differences in genetic sequences of viral genes or complete genomes to determine homology and detect variability that may alter viral replication and response to antiviral therapies. This last approach is referred to as genotyping. For some viruses, including HCV, there are no available cell culture systems or appropriate small animal models, making the characterization of these viruses by serotype or phenotype very difficult. Therefore, genotypic classification and description of viruses has come to prominence in virology and the treatment of infectious diseases.

Examination of the nucleotide sequence of a viral gene or complete genome is employed to generate information about the viral isolate that can be used in the clinic. In addition to the identification and classification of a viral isolate, the genotype may be used to detect mutations in the genome that may have consequences with regards to viral infectivity, pathogenesis or response to different antiviral agents. To obtain this sequence-based information, multiple technologies have been employed, including DNA sequencing, restriction fragment length polymorphisms (RFLP), line probe assays (LiPA) and, more recently, kinetic amplification with dissociation analysis [2–4]. All of these techniques share the requirement of an initial target amplification step to generate suitable amounts of template for genotypic analysis. This simple amplification step may have clinical implications [4]. If a patient has multiple viral quasispecies or is infected with multiple genotypes, the oligonucleotide primers used to generate the amplicon for genotypic analysis may amplify the viral isolate with the highest concentration in the serum or they may preferentially bind to...
a particular isolate. In either case, the clinical information generated by genotypic analysis would be limited to that particular isolate and would not provide appropriate insight into mixed infections or populations of viral quasispecies that may be present in the infected patient. Thus, regardless of the method selected to determine viral genotype, the information obtained must be evaluated in the context of the likelihood of other viral quasispecies existing in a patient and that genotyping may need to be repeated as the environment of the patient changes during treatment and disease progression [5–7].

The following review examines the clinical role of genotyping for HCV, with emphasis on how this genetic information is used to manage the treatment of patients with chronic hepatitis C.

Methods of determining HCV genotype

Due to the potential clinical implications of different HCV genotypes, reliable methods are required to classify and characterize viral genomes from primary patient isolates. The reference standard and most definitive method for determining genotype involves the direct sequencing of a specific polymerase chain reaction (PCR)-amplified portion of the viral genome obtained from a patient sample, followed by phylogenetic analysis. The NS5, core, E1 and 5' UTR regions of the HCV genome have been used to determine viral genotype using this method [4]. Sequencing, often of multiple regions of the viral genome, in combination with the generation of phylogenetic trees, results in an accurate classification of primary patient isolates [8,9]. Furthermore, sequencing methods provide complete information about the amplified region including the detection of polymorphisms within the viral genome that may or may not have clinical relevance. In the past, sequencing and phylogenetic analysis for the classification and characterization of HCV isolates was difficult to complete on a large scale and required technical expertise for this complex technology [10]. However, high-throughput capillary sequencers combined with comprehensive HCV sequence databases have made this method more suitable for clinical and laboratory environments. Similar to most genotyping methods, sequencing involves PCR amplification of target regions of the viral genome and is confined by the advantages and disadvantages associated with PCR. In addition, differentiating mixed genotypes from patient samples is a limitation for sequencing-based methods.

There are several alternative methods used to determine HCV genotypes. RFLP, which utilizes restriction enzymes to recognize genotype-specific cleavage sites in a PCR-amplified DNA fragment, has been applied to determine HCV genotypes [11]. PCR amplification with type-specific primers has been used to determine HCV genotype, but sensitivity and specificity parameters of this method require further evaluation [4,12,13]. DNA hybridization technologies, including LiPA, are commercially available to determine HCV genotypes [14–16]. In this method, PCR amplicons hybridize to genotype-specific probes immobilized on nitrocellulose strips or a 96-well microplate and are visualized using colorimetric chemistry. Simple interpretation of the banding pattern determines the viral genotype or the presence of known mutations. Genotype-specific antibodies have also been exploited to determine HCV genotypes [4]. These antibodies recognize the NS4 region of HCV and are employed in the form of an enzyme immunoassay (EIA). This type of serological genotyping is simple and has a low risk of contamination, but lacks specificity and sensitivity, which limits its clinical applications. Finally, kinetic PCR with fluorescence resonance energy transfer (FRET) probes or intercalating dyes has been utilized to detect and genotype HCV in a single tube reaction using dissociation curve analysis [3,17]. Further experimentation with this new technology is required to determine its reproducibility and to warrant expanded use in a clinical setting. Although all of these methods are able to identify the major groups of HCV, only direct nucleotide sequencing is efficient in discriminating among subtypes, detecting known mutations and elucidating new polymorphisms that may have clinical implications [4,18].

HCV: epidemiology, virology and genotypes

HCV infection is a major health problem throughout the world. Collective estimates indicate over 175 million people are infected with HCV worldwide with up to 4 million new infections each year [19,20]. The majority (75–85%) of HCV-infected individuals progress from acute to chronic hepatitis C [21]. Infection with HCV is the most common cause of progressive liver disease, including cirrhosis and hepatocellular carcinoma (HCC), in the United States and Europe and is the one of the most frequent reasons for liver transplantation [22]. HCV infection has been referred to as the ‘silent epidemic’ as the majority (75–80%) of infected individuals are asymptomatic or unaware of their infection and have not been tested for HCV [19,23]. HCV may be transmitted by percutaneous exposure to infected blood or blood products. As such, injecting drug users account for more than 50% of all new cases of hepatitis C with other modes of transmission, such as occupational exposure and mother-to-child transmission, accounting for the rest [19,21,24]. Although it is unlikely that HCV can be
transmitted through casual contact, there is evidence to suggest that hepatitis C may be spread via sexual intercourse, although with limited efficiency [25–29]. Finally, a major characteristic of infection with HCV is the absence of protective immunity following initial exposure to the virus. This has led to the identification of patients (1.6–45% of cases) with mixed HCV genotypes and has important implications with regards to vaccine development [19,30]. The silent incidence, modes of transmission, chronic disease progression, increasing burden to healthcare resources and projected increase in mortality attributed to HCV infection have caused clinicians to focus on this global health issue [31].

HCV is a unique, enveloped, positive, single-stranded RNA hepacivirus of the Flaviviridae family [32]. The RNA genome is approximately 9.6kb in length and encodes a single, large polypeptide that is post-translationally cleaved into multiple structural (core, E1 and E2) and non-structural (NS2–NS5) peptides. The virus replicates in the cytoplasm using an RNA-dependent RNA polymerase that lacks general proofreading ability [33]. This error-prone RNA polymerase is responsible for the genetic variability exhibited by HCV isolates and the spontaneous nucleotide substitution rate of HCV is high, with a frequency of $10^{-2}$ to $10^{-3}$ substitutions per nucleotide site per year [1,32]. In each infected individual, it is likely that HCV circulates as a mixture of genetically different but related quasispecies, differing by 1–5% in nucleotide sequence (Table 1) [5,33]. This population of variants permits rapid adaptability of the virus in the event of environmental changes and is one strategy utilized by the virus to escape selective forces such as antiviral agents or the immune system. The rapid production of these HCV quasispecies ($10^{10}$–$10^{12}$ virions per day), continuous cell-to-cell transmission and absence of a vigorous T-cell response promote persistent infection and progression towards chronicity [4,33].

Currently, all known HCV isolates have been divided into six phylogenetically distinct groups, referred to as clades, and more than 70 subtypes based upon nucleotide sequence and phylogenetic analysis [5,6,8,34,35]. To avoid confusion between different HCV nomenclature systems, Robertson et al. have recommended that HCV genotypes 1, 2, 4 and 5 be referred to as clades 1, 2, 4 and 5, respectively, with genotypes 3 and 10 forming clade 3 and genotypes 6, 7, 8, 9 and 11 forming clade 6 [36]. The merits of different nomenclature systems for HCV are debatable; however, for this review, the clade classification system will be applied. Classification of HCV isolates is achieved by employing a consensus system based on sequence homology in at least two regions of the viral genome with confirmation via phylogenetic tree analysis [1,8,34,37,38]. Departure from this system led to the identification and classification of HCV genotypes 7–11 [39]. However, re-analysis of these HCV genotypes using the consensus approach identified types 6, 7, 8, 9 and 11 as members of HCV clade 6 and types 3 and 10 as members of HCV clade 3 [9]. The amount of sequence diversity within these groups was greater than observed with the other HCV genotypes and subtypes indicating that, in the future, upon further molecular and clinical characterization, there may be some subtle differences between these subtypes that may justify alternative nomenclature. In general, viral isolates from the same HCV subtype (for example, 1a vs 1a) differ in nucleotide sequence by no more than 5–15% and from two distinct subtypes (for example, 1a vs 1b) by 10–30% (Table 1) [3,4,33]. The HCV viral genome is approximately 60–70% homologous between known isolates of different genotypes.

| Table 1. Sequence homology of whole genome and specific genes among HCV classifications [4,31,33] |
|---|---|---|---|
| Classification | Description | % Nucleotide homology of the complete genome [33,37] | % Nucleotide homology of E1, NS4 and NS5 [34] | % Nucleotide homology of NS5 [35] |
| Genotype | Genomic heterogeneity across different HCV isolates | 50–70 | 55–70 | 56–72 |
| Subtype | Closely related isolates within each of the major HCV genotypes | 70–85 | 70–85 | 75–86 |
| Isolate | Related variants within each of the HCV subtypes | 85–95 | NA | NA |
| Quasispecies | Complex of genetic variants within individual HCV isolates | 95–99 | 88–100 | >88 |
(for example, 1 vs 2). With regards to epidemiological and clinical relevance of these HCV genotypes, differences in geographical distribution, clinical presentation and disease outcome, as well as response to therapy, have been attributed to HCV genotypes.

Global distribution of HCV genotypes and clinical implications

Geographical differences appear to exist in the distribution of HCV genotypes (Table 2) [4,5,33,40,41]. Genotype 1a, the prototype sequence used in the development of early HCV diagnostic assays and frequently found associated with intravenous drug abuse, is most commonly detected in the United States and Europe. Genotype 1b, principally transmitted via blood transfusions and currently the most common genotype, is distributed worldwide with a high prevalence in the United States and Europe as well as Japan, where 1b is responsible for over 70% of cases of HCV infection [4,42]. Genotypes 2a and 2b, representing 10–30% of global HCV types, are common in North America, Europe and Japan, while genotype 2c is found in Northern Italy. Genotype 3 is most prominent in the Indian subcontinent as well as Southeast Asia and Indonesia. Of interest, subtype 3a is particularly prevalent in injecting drug users in Western Europe and the United States, and, in combination with genotype 1a, accounts for 70% of new HCV infection cases due to the efficient route of transmission [4,43]. Genotype 4 appears to be prevalent in North Africa and the Middle East, while genotypes 5 and 6 are most frequently reported in South Africa and Hong Kong, respectively [44]. Although the global distribution of HCV genotypes can be summarized in this fashion, the prevalence of HCV genotypes may vary in urban settings with immigrant populations, where less common genotypes may be locally predominant. Furthermore, the prevalence of HCV genotypes and subtypes may also vary in major metropolitan areas that serve as centres for travel and which tend to have greater numbers of injecting drug users [45]. In addition, a portion of HCV-infected patients have mixed genotypes and subtypes, with 1a and 1b being the most common mixture [33]. These mixed infections may be more common than first thought and may be an important factor associated with the immune response to HCV infection and response to therapy [46].

The geographical distribution of HCV genotypes may be useful for epidemiological purposes as well as having clinical management implications [4]. HCV genotyping may offer a method for tracing the source of an HCV outbreak in a population. For example, HCV genotype determination would be useful to trace HCV infection in patients with identical isolates back to a common source, such as contaminated blood products or surgical instruments [47,48]. The geographical prevalence of HCV genotypes may generate insight into alternative modes of viral transmission through monitoring the incidence of rare HCV genotypes when they are introduced via immigration or travel [45]. In addition, the global distribution of HCV genotypes may have clinical implications as response to therapy, and possibly disease progression, differs among the HCV clades [4,5,33,49].

Regions that have predominant HCV genotypes that do not typically respond well to available therapies or tend to progress to advanced liver disease will have to confront different issues with regards to the long-term management and burden on healthcare resources than areas with responsive HCV isolates. Furthermore, areas of the world where the predominant HCV genotype is not 1a or 1b may be limited in their use of HCV diagnostics and the reliability of the results from assays developed based upon the detection of genotype 1a [4]. First generation EIA, as well as qualitative and quantitative HCV RNA assays, were based on genotype 1 and lacked sensitivity for the detection of non-1 HCV isolates. The current generation of EIAs has improved sensitivity as well as specificity and tends to be less influenced by the infecting genotype. The latest versions of the HCV RNA assays used for viral detection, quantification and genotyping have been reported to have equal sensitivity for members of the six clades of HCV [50,51]. However, the sensitivity and reliability of some of these HCV RNA assays are influenced by the region of the HCV genome amplified for analysis and primer design. Any genotype-dependent

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associated liver disease. However, similarly designed genotype 1b is a potential marker for more severe HCV-
[4,67,68]. Collectively, these studies would suggest that patients when compared with the other HCV genotypes to rapid recurrence and severe hepatitis in transplant of HCC [63–66]. Finally, genotype 1b has been linked HCV genotype 1b and the frequency and development have provided data indicating a relationship between [4,41,49,60–62]. Furthermore, several investigations decompensated liver disease requiring transplantation type 1b and the development of cirrhosis and evidence suggesting an association between HCV geno-
ty, severe liver disease and a more aggressive clinical course than other HCV genotypes [59]. Zein et al., as well as other groups, have provided indirect evidence suggesting an association between HCV genotype 1b and the development of cirrhosis and decompensated liver disease requiring transplantation [4,41,49,60–62]. Furthermore, several investigations have provided data indicating a relationship between HCV genotype 1b and the frequency and development of HCC [63–66]. Finally, genotype 1b has been linked to rapid recurrence and severe hepatitis in transplant patients when compared with the other HCV genotypes [4,67,68]. Collectively, these studies would suggest that genotype 1b is a potential marker for more severe HCV-associated liver disease. However, similarly designed investigations have not arrived at the same conclusions for genotype 1b and further studies will be required to elucidate any role of HCV genotype in disease progression or severity [52,69–76].

HCV genotypes, clinical presentation and disease progression
In general, it appears that members of the HCV clades do not differ in clinical presentation and are not related to distinctive clinical conclusions or severity of illness [5,22,52]. Patients infected with any HCV genotype can develop advanced liver disease, including cirrhosis and HCC, and the frequency of these complications appears to be similar across the six HCV clades. Furthermore, there is significant variation of HCV-related disease from patient to patient infected with similar HCV genotypes. Therefore, it is unlikely that HCV genotype can be used as a prognostic marker for HCV infection and prediction of disease outcome [5]. The outcome of infection with HCV and the progression of liver disease are probably decided by a combination of host and viral factors including the innate, cellular and humoral immune responses, competent viral replication and efficient cell-to-cell transmission, as well as potential adaptability of the HCV quasispecies population in the host environment.

The topic of HCV genotypes and their role in liver lesions, disease progression and clinical outcome does have some interesting perspectives and is not without controversy. Steatosis, the accumulation of fat within hepatocytes associated with chronic infection, occurs regardless of HCV genotypes and tends not to regress after successful antiviral therapy [53]. However, in patients infected with HCV genotype 3a, resolution of viral infection is associated with disappearance of steatosis, indicating that, in these patients, steatosis may be considered as a genotype-related HCV-induced cytotoxic lesion [33,34–58]. In addition, there are a number of small investigations that suggest HCV genotype 1b may be associated with progression to chronicity, severe liver disease and a more aggressive clinical course than other HCV genotypes [59]. Zein et al., as well as other groups, have provided indirect evidence suggesting an association between HCV genotype 1b and the development of cirrhosis and decompensated liver disease requiring transplantation [4,41,49,60–62]. Furthermore, several investigations have provided data indicating a relationship between HCV genotype 1b and the frequency and development of HCC [63–66]. Finally, genotype 1b has been linked to rapid recurrence and severe hepatitis in transplant patients when compared with the other HCV genotypes [4,67,68]. Collectively, these studies would suggest that genotype 1b is a potential marker for more severe HCV-associated liver disease. However, similarly designed investigations have not arrived at the same conclusions for genotype 1b and further studies will be required to elucidate any role of HCV genotype in disease progression or severity [52,69–76].

HCV genotype and response to therapy
The main objective of therapy administered to patients with chronic hepatitis C is to achieve a sustained virological response (SVR) characterized by the clearance of serum HCV RNA at the end of therapy and maintained throughout the 6-month follow-up period after completion of treatment [77]. The relationship between HCV characteristics and response to therapy has been clarified through multivariate analysis of viral, host and clinical factors. HCV genotype is an important viral factor that has been identified as a strong independent predictor of SVR to therapy [19,20,22,33,78–80]. The current standard of care for chronic hepatitis C includes standard (STD) or pegylated (PEG) interferon-α (IFN-α) administered as a monotherapy or in combination with ribavirin [81]. Response to IFN-α therapy differs among HCV genotypes, with response rates among patients with genotypes 2 and 3 observed to be two- to threefold higher than in individuals infected with genotype 1, regardless of the therapeutic schedule [33,79,80,82]. This trend is maintained upon re-treatment of non-responders, as 50–60% of patients infected with HCV genotypes 2 or 3 who failed initial IFN-α therapy achieved an SVR upon re-treatment with PEG-IFN-α and ribavirin compared with 14% of individuals infected with genotype 1 [83]. The limited efficacy of IFN-α to block viral replication and the reduced rate of sustained HCV clearance observed in patients infected with HCV genotype 1 is clinically important [84,85]. Therapy for patients with chronic hepatitis C and infected with genotypes 2 or 3 has been optimized for a duration of 24 weeks rather than the 48 weeks required to treat genotype 1 [22]. Furthermore, a high rate of SVR in patients infected with HCV genotypes 2 and 3 is achieved using a lower dose of ribavirin as well as PEG-IFN-α compared with individuals infected with genotype 1 [86,87].

This difference in response to IFN-α therapy across genotypes has been incorporated into consensus guidelines for the treatment of patients with chronic hepatitis C and should be considered as the current standard of care (Figure 1) [21,22,88]. The therapeutic response rates attributed to members of clades 4, 5 and 6 as well as HCV subtypes are not as well defined as with clades 1 to 3. Currently, patients infected with these less prevalent HCV genotypes are treated in a similar manner as individuals infected with genotype 1. There are investigations involving small groups of hepatitis C patients infected with members of clades 4,
5 or 6 that provide some insight into virological response to IFN-α therapy [18,89,90]. For example, a recent study compared the virological response of patients infected with either genotype 6 (n=16) or genotype 1 (n=24) and treated with a combination of STD-IFN-α-2b with ribavirin for 12 months. Patients with genotype 6 had a better end-of-treatment response (75% vs 41.6%) as well as better rates of SVR (62.5% vs 29.2%) than subjects infected with HCV genotype 1 [91]. Further studies examining larger populations of patients infected with these less common HCV genotypes and placed on IFN-α therapy are required to elucidate differences in virological response that would determine optimal therapeutic regimens.
The molecular basis for this difference in response rates among HCV clades has not been clearly defined. As mentioned earlier, one of the key characteristics of HCV is the genetic variability generated via an error-prone RNA-dependent RNA polymerase resulting in a circulating population of related, but different, HCV quasispecies. The variability in HCV genome sequence and potential changes to viral protein structure and function among genotypes and quasispecies could account for the differences in sensitivity to IFN-α therapy [5,92]. To date, identification and characterization of viral proteins that determine therapeutic response has been limited and tentative. Several investigations have focused on the NS5A region of the HCV genome as well as the corresponding protein. These studies suggest that the NS5A protein is involved in viral replication and could curtail the antiviral action of IFN-α therapy. Furthermore, the mechanism for this resistance appears to involve the inhibition of IFN-α-induced protein kinase R (PKR) by NS5A and its PKR-binding domain [32,93]. However, these observations are not without controversy and other regions of the HCV genome, including alternative mechanisms, have been proposed to be involved in HCV resistance to IFN-α therapy [94–98]. Further investigations examining both host and viral factors are required to define the molecular mechanisms responsible for the improved response of patients infected with HCV isolates from clades 2 and 3 compared with other genotypes.

Other clinical implications of HCV genotypes

In addition to the lack of appropriate cell culture and small animal models, the existence of distinct HCV genotypes with antigenic variability complicates the development of an effective prophylactic or therapeutic vaccine [5]. The factors that contribute to an effective immune response against HCV have not been clearly defined but it is likely that both humoral and cellular immunity will need to be generated through vaccination [99]. However, neutralizing epitopes are among the most distantly related sequences across different HCV genotypes, probably contributing to the lack of protective immunity following multiple exposures to HCV, the number of patients with mixed genotypes and re-infection of individuals who have recovered from HCV infection in the past [5,6,9]. These observations underline the quasispecies nature of HCV and the selection of strains to avoid immune surveillance [4]. Regions of the core protein, the NS3 protein and the hypervariable region (HVR1) located towards the N-terminus of the HCV E2 protein have been implicated as possible targets for HCV-specific cytotoxic T-lymphocyte (CTL) recognition [100–104]. However, single amino acid changes within these epitopes can result in a failure of recognition by HCV-specific CTLs.

Development of an effective vaccine for HCV will need to account for the genetic differences between HCV clades and the variability observed within HCV quasispecies to escape immune surveillance [105].

In summary, the relevance of determining HCV genotype in a clinical setting is evident. HCV genotypes have different but predictable responses to IFN-α-based therapies and these differences have been summarized in treatment guidelines that account for duration and dose of therapy. Using any one of a number of methods, HCV genotype is determined early in the treatment of patients with chronic hepatitis C to assist physicians with their decision of dosage and duration of therapy. For instance, patients infected with HCV genotypes 2 and 3 are treated with PEG-IFN-α and ribavirin for only 24 weeks and at lower doses of both compounds compared with the other genotypes, which require a longer period of treatment (48 weeks) and higher concentrations of combination therapy. Determination of HCV genotype can help prepare the clinician and patient for the expectations and complications of the prescribed treatment regimen. By extension, knowledge of the distinct geographical distribution of HCV genotypes can help healthcare systems prepare for the resources and financial commitments required to treat predominant genotypes in their region and the application of appropriate treatment guidelines. Further investigations are required to provide definitive insight into the role of HCV genotypes and subtypes in disease progression and into how differences in these genotypes effect response to therapy and permit escape from immune surveillance.

Summary and future directions

Chronic viral hepatitis and the complications associated with progressive liver disease are a global health problem. One of the major causative agents, HCV, has been classified into distinct clades, genotypes and subtypes based upon sequence analysis of their respective genomes along with determination of phylogenetic relationships between the natural variants (Table 3). Genotypes of HCV have distinct geographical distributions. A clear understanding of regional genotypes as well as global migration patterns may help governments and healthcare systems prepare the resources required to treat the predominant HCV genotype infecting individuals in their regions. Currently, determination of HCV genotype has direct clinical implications for duration and dosage of combination therapy including PEG-IFN-α with ribavirin. However, the detection of drug-resistant mutations or natural polymorphisms in the HCV genome that affect response to therapy is not widespread as alternative treatment options available for patients with chronic
hepatitis C are currently limited. It is clear that well-designed studies are required to provide definitive insight into the role of HCV genotypes in disease progression for patients with chronic hepatitis.

References


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