What You Need to Know About GB Virus C

Sarah L. George, MD and Dino Varmaz, BA

Address
Division of Infectious Diseases, Saint Louis University School of Medicine, FDT-BN, 3635 Vista Avenue, St. Louis, MO 63110, USA.
E-mail: georgesl@slu.edu

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Introduction

GB virus C (GBV-C) is a nonpathogenic member of the Flaviviridae family most closely related to hepatitis C virus (HCV). Infection is common in healthy and immunocompromised people and may persist for years. GBV-C infection is associated with improved survival, improved AIDS-free survival, higher CD4+ T-cell counts, and lower HIV viral loads in HIV-infected people compared with people infected with HIV but not GBV-C. The mechanism of this effect is not yet clear, but GBV-C has been shown to inhibit HIV replication in vitro through increased synthesis and secretion of anti-HIV β-chemokines MIP-1α, MIP-1β, RANTES, SDF-1, and SDF-2 and downregulation of CCR5 receptor expression. GBV-C also inhibits apoptosis of its host cell, similar to HCV. GBV-C E2 protein in serum has also been associated with prolonged survival in HIV infection; recent evidence indicates that GBV-C E2 protein may neutralize HIV infection in vitro.

GBV-C Virology and Replication

GB virus C is a member of the Flaviviridae family, which includes such pathogens as HCV, dengue, yellow fever virus, and West Nile Virus, as well as the non-pathogenic tamarin viruses GBV-A and GBV-B (Fig. 1). The virology of GBV-C is best understood in comparison with closely related HCV, with which it shares approximately 25% amino acid sequence homology [2]. The two viruses have approximately 9600 nucleotide (HCV) and 9400 nucleotide (GBV-C) positive polarity RNA genomes encapsidated within enveloped virions. Each genome encodes a single long open reading frame, which is translated into a polyprotein, which is in turn cleaved by cellular and viral proteases to produce mature viral proteins. Structural proteins consist of the E1 and E2 surface glycoproteins. GBV-C E2 protein lacks the hypervariable region found in the amino terminus of the HCV E2 protein. Although biophysical analysis of GBV-C virions implies that they contain a protein capsid, the obvious sequences encoding the core protein have not been identified in the GBV-C genome [8]. Plasma-derived GBV-C particles visualized by electron microscopy demonstrate enveloped particles with a nucleocapsid structure [9], but the source and sequence of the visualized nucleocapsid remains unknown. Nonstructural GBV-C proteins and their putative functions consist of NS2 (protease), NS3 (serine protease/RNA helicase), NS4, NS5A, and NS5B (RNA-dependent RNA polymerase). NS5A protein, by analogy with HCV, is thought to play a role in regulating host immune response to GBV-C. The coding region is flanked by a 5’ nontranslated region (5’ntr), which initiates translation and a 3’ non-coding region (3’ntr), which regulates viral transcription.

It is presumed by analogy with HCV that GBV-C infects its host cell through interaction between the E1/E2 surface glycoproteins with an as-yet unidentified cellular receptor(s), the survival benefit of GBV-C in HIV infection, GBV-C’s inhibition of HIV replication, immunomodulatory functions, and future research directions.
followed by endocytosis, de-encapsulation, protein translation, and synthesis of a full-length negative strand replication intermediate, followed by transcription of new positive strand polarity viral genomes. Daughter virions are presumed to be encapsidated within newly synthesized envelope proteins and exit the cell. It should be emphasized that none of these processes have yet been directly visualized and are presumed based on analogy with other flaviviruses.

GB virus C appears to be less genetically diverse than HCV because no hypervariable region is found in the NH2 terminus of the E2 gene, quasispecies analyses reveal lower variability than is observed for HCV [10,11], and only four GBV-C genotypes have been identified [12,13], compared with six genotypes and multiple sub-genotypes for HCV [14,15]. Sequences of different genotypes of HCV may differ by up to 30%, whereas GBV-C genotypes differ by only 14% [16]. The geographic distribution of GBV-C genotypes mirrors that of human racial groups, indicating that GBV-C may have infected the ancestral human population in Africa and diversified concurrently with human migrations. GBV-C genotype 1 is found in Africa and has relatively diverse 5' ntr sequences, whereas genotype 2 is prevalent in Europe and in North American descendants of European populations. Genotype 3 is found in northern Asia and native populations of South America, and genotype 4 in southern Asia [12,16].

The site or sites of GBV-C replication in vivo have not been established conclusively. Negative-strand RNA is a necessary intermediate in GBV-C replication and has been found in liver biopsies using in situ hybridization, but the number of infected hepatocytes is 100-fold lower than is found in HCV-infected liver [17]. Also, the liver-to-serum ratio of GBV-C RNA is low (often less than 1) [18–20], unlike the high liver–serum RNA ratio of HCV [21,22]; this is consistent with a predominantly extrahepatic site of GBV-C replication. Negative-strand GBV-C RNA has been amplified by polymerase chain reaction (PCR) from peripheral blood mononuclear cells (PBMCs) [23], CD4+ T cells [24], bone marrow [25,26], lymph node [27], and spleen [26,27]. George et al. productively infected PBMCs, B lymphocytes, and CD4+ and CD8+ T lymphocytes with GBV-C in vitro and cultivated GBV-C in the same cell types isolated from a GBV-C–infected person (Manuscript in preparation). Thus, GBV-C appears to be pan-lymphotropic but may also replicate at lower levels in liver. Consistent with this observation, GBV-C has been cultivated at least transiently in vitro in liver- and lymphocyte-derived cell lines such as Huh-7, HepG2, Daflu cells (an interferon-resistant CD4 cell line), MT-2 cells, and MOLT-4 cells [24]. GBV-C replication in vivo produces viral RNA levels of 102 to 107 copies/mL serum in immunocompetent hosts, 104 to 107 copies/mL serum in immunocompromised hosts [23,28], and up to 108 copies/mL in HIV-infected hosts [29,30].

**Natural History of GBV-C Infection in Humans**

GB virus C can be transmitted by exposure to infected blood, through sexual intercourse, and vertically from infected women to their newborns, but the efficiency of transmission by the various routes can differ greatly [31]. Because of the similar routes of transmission, coinfection of GBV-C with HCV and/or HIV is common, with GBV-C viremia found in 15% to 35% of HCV-seropositive people and 25% to 40% of HIV-seropositive people. Serologic evidence of prior infection with GBV-C (GBV-C E2 antibody) is found in 30% to 60% of HCV-seropositive individuals [32] and 30% to 65% of HIV-seropositive people. In HIV patients, the prevalence of GBV-C viremia reaches depends in part on HIV acquisition risk factors [33]. HCV and GBV-C establish persistent infections that can last for life. The rate of chronicity following acute infection with GBV-C in healthy populations is not precisely known but is estimated to be approximately 25% to 50% [1]. GBV-C and HCV have similar rates of nucleotide substitution during persistent infection (0.4–1.9 × 10–3 for HCV and 0.4–2.4 × 10–3 for GBV-C). GBV-C infection results in three possible outcomes: 1) persistent infection, which can last for decades; 2) clearance of GBV-C RNA from serum concurrently with development of E2 antibody to GBV-C; and 3) clearance of GBV-C RNA from serum without development of E2 antibody. To establish long-lasting chronic infections, GBV-C must be able to persistently evade the immune system, but the evasion mechanism(s) employed are unknown [34].

Most healthy people ultimately clear GBV-C infection; unlike in HCV infection, protection from GBV-C infection and clearance of viremia are usually associated with appearance of antibodies to the E2 glycoprotein [32,35]. In a study of 75 GBV-C anti-E2 antibody–positive intravenous drug users followed over 10 years, 94% retained detectable anti-