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Role of GB virus C in modulating HIV disease

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Abstract

GB virus C (GBV-C) is a member of the *Flaviviridae* family and the most closely related human virus to HCV. However, GBV-C does not replicate in hepatocytes, but rather in lymphocytes. GBV-C has a worldwide distribution and is transmitted sexually, parenterally and through mother-to-child transmission. Thus, co-infection with HCV and HIV is common. Until now, no human disease has been associated with GBV-C infection. However, there are several reports of a beneficial effect of GBV-C on HIV disease progression *in vivo*. Different mechanisms to explain these observations have been proposed, including modification of antiviral cytokine production, HIV co-receptor expression, direct inhibition of HIV-1 entry, T-cell activation and Fas-mediated apoptosis. Further understanding of these mechanisms may open new strategies for the treatment of HIV/AIDS.

Keywords

co-infection; GBV-C; HCV; HIV

In 1995, Abbott Laboratories reported experimental infection of tamarins with two transmissible agents – GB virus A (GBV-A) and GB virus B (GBV-B) – initially obtained from the serum of a surgeon (initials GB) with non-A, non-B hepatitis [1]. Using degenerate primers and human sera containing antibodies recognizing GBV-A and/or GBV-B recombinant proteins a novel virus was identified, tentatively named GBV-C [2]. Another independent research group discovered novel viral sequences extracted from the serum of a patient with cryptogenic hepatitis naming the virus hepatitis G (HGV) [3]. The genomes of GBV-C and HGV were found to share more than 95% homology, representing two variants of the same virus [4]. GBV-C/HGV was initially considered a possible cause of hepatitis [5]. However, no association between GBV-C/HGV and chronic hepatitis or any other human disease has been confirmed subsequently (reviewed in [6]). Therefore, in this review the virus will be referred to as GBV-C.

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GBV-C: transmission, epidemiology & detection

The modes of transmission of GBV-C are through sexual contact [7–9], parenterally after exposure to blood or blood products [3,10,11] and less frequently vertically from mother-to-child [12,13]. GBV-C has a worldwide distribution and is commonly found in the general population [14]. Up to 4% of healthy blood donors in Western countries are GBV-C viremic [15–17], while in developing countries the prevalence of GBV-C approaches 5–18% in the general population [18–22]. Among populations at high risk for other parenterally transmitted viruses, such as HBV, HCV or HIV, the GBV-C prevalence approaches 50% [15,23–25]. The temporal relationship between GBV-C persistence and clearance of GBV-C RNA in the blood is unknown. Generally, immunocompetent individuals eliminate GBV-C within the first years following infection [26–28]. However, in some individuals, GBV-C replication may persist for decades [23]. Clearance of GBV-C is commonly associated with the development of antibodies against the E2 region [29–31]. GBV-C E2 antibodies are two- to six-times more prevalent than GBV-C RNA and protect against re-infection with GBV-C to some extent [26,31] (reviewed in [32]). However, there are cases in which GBV-C clearance does not result in the development of E2 antibodies [33–35]. In immunocompetent individuals, GBV-C RNA and E2 antibodies are rarely detected in the blood simultaneously, and when this does occur, it is usually a transient condition [24].

GBV-C replication is detected by nucleic acid amplification [15], and quantified by terminal dilution methods [36], branched chain DNA assays [37], real-time PCR [38] or competitive real-time PCR [39]. Unfortunately, no commercial assay for the detection of GBV-C E2 antibodies is currently available. Future development of a GBV-C E2 antibody assay is very much needed in order to provide better insight into GBV-C infection status and thereby enabling better analysis of the impact of GBV-C infection on other viral diseases [40,41].

GBV-C: virology

GBV-C shares approximately 30% amino acid homology with HCV [5,32]. GBV-C consists of a positive-sense, ssRNA genome of approximately 9400 nucleotides. The 5′ untranslated region contains an internal ribosomal entry site and is followed by a single long open reading frame encoding for a multifunctional polyprotein of approximately 3000 amino acids (reviewed in [42]). This polyprotein is co- and post-translationally cleaved by viral and cellular proteases resulting in several structural and nonstructural viral proteins [3,5,43,44]. The structural proteins of GBV-C include two envelope glycoproteins (E1 and E2), while the nonstructural proteins include NS2 (a protease), NS3 (a RNA helicase and trypsin-like serine protease), NS4, NS5A and NS5B (a RNA-dependant RNA polymerase) [5]. However, it should be noted that nearly all of these data are inferred by sequence alignment and comparison with the genomic structure of HCV; therefore, divergent functions are plausible.

The exact site(s) of GBV-C replication has not been established firmly. GBV-C RNA replication has been described in the liver and localized in hepatocytes [45,46]. *In vitro* replication of GBV-C in human hepatoma cell lines suggested hepatotropism [47,48]. By contrast, a study by Laskus *et al.* does not confirm these findings [49]. Moreover, GBV-C RNA has been detected in peripheral blood mononuclear cells (PBMCs), spleen and bone marrow suggesting lymphotropism [50–52]. More recently, GBV-C has been shown to replicate in primary T and B lymphocytes and in PBMCs *in vitro* [36,53]. Thus, GBV-C tropism is still a matter of debate, but appears to be primarily lymphotropic [54,55].

GBV-C: genotype diversity

On the basis of the predicted genomic structure and relatedness to other viruses, the GB viruses have been classified as members of the *Flaviviridae* family. As GBV-B induced

hepatitis in experimentally infected tamarins it has been classified with the various hepatitis C genotypes within the *Hepacivirus* genus [56], while a more recent report suggests that GBV-A, GBV-C and the distantly related GBV-D in bats should be classified within the newly proposed *Pegivirus* genus [57].

Phylogenetic analysis of the 5′ untranslated region and the *E2* gene suggests the existence of at least six distinct genotypes of GBV-C [58]. GBV-C genotypes show a worldwide geographical clustering, suggesting an evolutionary history paralleling prehistoric human migration [59,60]. Genotype 1 is common in Africa and North America, genotype 2 in North/South America and Europe, genotype 3 in Asia and South America, genotype 4 in southeast Asia, genotype 5 in South Africa and a sixth genotype was more recently found in Indonesia [58,61–67]. Within a given genotype, additional diversity exists. For example, intragenotype genetic distances may range from 13 to 19% and multiple subtypes within a genotype have been reported [68–70]. Moreover, mixed infections and recombinant viruses have been detected [71–73]. Within an individual, distinct variants of GBV-C have also been identified implying that viral adaptation may occur within individuals as well [74–78]. Interestingly, interferon sensitivity and cell tropism may differ among such variants [78–80]. Similarly, clinical isolates of GBV-C also vary in their ability to replicate in culture [80,81], suggesting that genotypic diversity may impact virologic phenotype. While the biological consequences of recombination and intrapatient diversity to GBV-C pathogenesis have not been examined, studies of HIV suggest that viral diversity may result in altered cell tropism, virulence and/or drug susceptibility [82].

GBV-C: impact of co-infection on HIV disease

In 1998, two reports raised interest on GBV-C in HIV disease. Toyoda *et al.* first reported that GBV-C co-infection had no adverse effect on the clinical course of HIV in a cohort of 41 HIV-positive Japanese patients with hemophilia [83]. GBV-C viremia was detected in 11 (27%) out of the 41 patients. Interestingly, patients co-infected with GBV-C showed lower mean HIV RNA levels. Moreover, there was a nonsignificant trend towards slower progression to AIDS and improved survival. In the same year, Heringlake *et al.* studied 197 HIV-positive German patients, of which 33 (17%) were GBV-C viremic [84]. They showed that higher baseline CD4 cell counts, slower progression to AIDS and improved survival were associated with GBV-C co-infection. These observations attracted much interest and were supported further by subsequent studies [85–87]. Similarly, in HIV patients receiving highly active antiretroviral therapy (HAART), Tillmann *et al.* reported a significant survival benefit of GBV-C infection on progression to AIDS [88]. An inverse relationship between GBV-C and HIV viral load was reported, suggesting an inhibition of HIV replication by GBV-C. In patients on HAART, Bjoerkmann *et al.* found that median GBV-C RNA levels increased, whereas GBV-C RNA levels decreased upon interruption of HAART and subsequent resumption of HIV replication, suggesting a reciprocal correlation between GBV-C and HIV viral dynamics [89]. Other studies demonstrated an improved initial response to HAART [90,91], a reduced risk of HIV viral rebound after initiating HAART [92] and a better quality of life in persons co-infected with GBV-C (Box 1) [93]. However, in the past several years, there has also been some controversy regarding the effects of GBV-C on the course of HIV infection, as some reports have failed to confirm a positive impact of GBV-C co-infection on HIV disease. Birk *et al.* studied 157 HIV-positive patients early after HIV seroconversion [94]. Among 36 (23%) patients co-infected with GBV-C, there was no impact of GBV-C co-infection on immunological and clinical outcomes of HIV-1 infection. Another study followed 230 HIV patients and detected GBV-C viremia in 62 patients (27%) [95]. GBV-C co-infection did not predict HIV outcome and no association of GBV-C viremia with the development of AIDS, HIV-related mortality or overall

mortality was seen. Both studies included patients before effective antiretroviral treatment was available, possibly explaining conflicting results.

Box 1

Impact of GB virus C co-infection on HIV

- Lower HIV-1 RNA levels
- Higher CD4 cell counts
- Slower progression to AIDS
- Improved response to HAART
- Better quality of life
- Reduction of mortality

HAART: Highly active antiretroviral therapy.

Several reports have explored the impact of GBV-C genotype on HIV disease progression. For example, Muerhoff *et al.* reported that CD4 cell counts were lower in HIV co-infected patients infected with GBV-C 2a than in patients with subtype 2b; however, other genotypes were not circulating at a sufficiently high prevalence for comparison among all GBV-C genotypes [96]. Subsequently, during HIV/HCV/GBV-C triple infection, GBV-C genotype 2 was associated with higher CD4 cell counts compared with GBV-C genotype 1 [97]. While similar findings have also been reported in a Brazilian cohort [67], a comparison of GBV-C genotype 2 versus non-2 infections in an Australian cohort observed no such difference in CD4 cell counts [98]. Thus, it is possible that GBV-C genotype could differentially impact HIV disease progression; however, further investigation in larger cohorts with multiple circulating GBV-C genotypes is warranted.

Differential effects of GBV-C co-infection in early versus advanced HIV infection may further explain the discrepancies reported regarding the association of GBV-C co-infection and HIV patient survival. In 2001, Xiang *et al.* reported that the beneficial effect of GBV-C co-infection was most pronounced among HIV patients with advanced immunodeficiency and CD4 T-cell counts <200/l [87]. This was further supported in the Multicentre AIDS Cohort Study in which no statistically significant effect of GBV-C co-infection on patient survival was observed early (12–18 months) after HIV seroconversion, whereas persistent GBV-C viremia over 5–6 years after seroconversion was associated with a significant survival benefit [33]. Likewise, in the Amsterdam Cohort Study, Van der Bij *et al.* observed that persistent GBV-C viremia was associated with prolonged survival [34]. In a meta-analysis evaluating the effect of GBV-C co-infection in late HIV disease, the authors found a significant reduction of mortality in HIV patients with GBV-C viremia [99]. Thus, differential effects of GBV-C co-infection in early versus late HIV disease may also account for the contradictory results regarding the association of GBV-C co-infection and patient survival.

Impact of GBV-C on HIV/HCV co-infection

Past or current GBV infection does not impact HCV replication, liver disease progression or response to interferon treatment in persons with HCV mono-infection [100–104]. However, a limited number of studies have reported a deleterious [105] or beneficial [106,107] impact of GBV-C on liver disease in the context of HCV mono-infection. While GBV-C has no reported impact on the outcome of HCV mono-infection, HIV clearly has a significant

negative impact on HCV disease progression. For example, HCV RNA levels are significantly elevated during HIV/HCV co-infection compared with HCV mono-infection [108,109]. Moreover, HCV-related liver fibrosis, cirrhosis and end-stage liver disease are accelerated during HIV/HCV co-infection [109–118]. This is particularly relevant as HCV infection has emerged as an important cause of morbidity and mortality in HIV-infected individuals [114,119,120]. Similar to HCV, GBV-C is also sensitive to the antiviral effects of interferon [100,101,121,122]. Thus, it is important to consider how the sum effects of HIV/HCV/GBV-C triple infection may impact HIV disease progression, as well as liver-related disease. Particularly in persons receiving IFN treatment, clearance of GBV-C RNA could have a negative impact on HIV-related outcomes. In a recent study evaluating the efficacy of IFN-α-2a plus ribavirin (RBV) versus pegylated IFN-α-2a plus RBV for chronic HCV infection in individuals co-infected with HIV [97], GBV-C RNA was cleared in 50% of HIV/HCV/GBV-C triple infected patients treated with IFN (or pegylated IFN) plus RBV [97]. Interestingly, GBV-C clearance was not associated with a short-term loss of HIV control. Similar results have been reported elsewhere [123], although studies with longer follow-up periods will be necessary to determine whether IFN treatment-induced clearance of GBV-C has deleterious effects on long-term HIV disease progression.

GBV-C: possible molecular interactions with HIV

The exact mechanisms by which GBV-C inhibits HIV replication remain obscure, although recent research has identified several possible pathways (reviewed in [124]). The currently postulated mechanisms by which GBV-C may lead to a beneficial effect on the course of HIV infection are summarized in Figure 1.

Altering the cytokine profile

Numerous studies have underlined the importance of Th1 and Th2 helper T cytokine response in HIV infection, demonstrating that progression of HIV disease is associated with a shift from Th1 to Th2 cytokine profile [125], which can be reversed after initiating HAART [126]. Nunnari *et al.* showed that GBV-C co-infection alters the cytokine profile in HIV infection [127]. GBV-C viremia in HIV patients resulted in more stable Th1 cytokine serum levels (IL-2 and -12) compared with HIV patients without GBV-C infection in whom Th1 cytokine levels decreased and shifted towards Th2 cytokines (IL-4 and -10) over time. Further more, endogenous levels of IFN-γ were found to be higher in PBMCs from GBV-C/HIV co-infected subjects compared with HIV mono-infected patients [128]. GBV-C also induced expression of IFN-γ and downstream IFN response genes in PBMCs [129]. GBV-C infection results in increased cell number and activation levels of circulating $CD80^+$ plasmocytoid dendritic cells (pDCs) in HIV patients, which are a major source of IFN-γ and other Th1 cytokines. It has been shown that pDCs are important in controlling HIV replication and high levels of HIV viral load are associated with pDC cell death via apoptosis and necrosis [130]. By preserving and boosting the innate antiviral response to infection with HIV, GBV-C may stabilize the antiviral response to HIV.

Modifying the expression of HIV co-receptors

HIV-1 entry into target cells depends, in addition to CD4, on its interaction with a secondary receptor, usually the chemokine receptors CCR5 or CXCR4. The β-chemokines MIP-1α and MIP-1β and RANTES (regulated on activation, normal T-cell expressed and secreted) are the natural ligands of CCR5, whereas SDF-1 and -2 are the natural ligands for CXCR4. In cultures of PBMCs, co-infection with HIV and GBV-C resulted in inhibition of HIV replication, as measured by the detection of p24 antigen in culture supernatants [80,87,131,132]. In further studies, expression of the NS5A phosphoprotein in a $CD4^+$ Jurkat T-cell line led to a dose-dependent inhibition of HIV replication [133]. NS5A resulted

in the release of SDF-1, thereby decreasing surface expression of CXCR4, partially explaining the observed inhibition of HIV replication. The NS5A protein from GBV-C genotypes 1, 2, 3 and 5 inhibited HIV replication [134]. This effect was related to NS5A amino acids 152–167 [135]. Interestingly, not only the NS5 protein from GBV-C but also from other members of the *Flaviviridae* family such as HCV, West Nile virus and yellow fever virus show inhibition of HIV replication [136].

Furthermore, GBV-C infection of PBMCs resulted in elevation of mRNA expression, not only for SDF-1, but also for RANTES, MIP-1α and MIP-1β, and higher secretion into culture supernatants, leading to lower surface expression of CCR5 [131]. Antibodies directed against these chemokines neutralized the inhibitory effect of GBV-C on HIV [131]. GBV-C E2 protein was shown to bind to CD81 (a member of the tetraspanin family) on the cell surface of $CD4^+$ T lymphocytes *in vitro* [137]. This induced a dose-dependent release of RANTES and down-regulation of CCR5 surface expression, which was also found in GBV-C/HIV co-infected patients. However, direct interaction of GBV-C E2 with CD81 could not be confirmed by others [138]. Interestingly, in GBV-C/HIV co-infected patients in advanced stages of immunodeficiency, reduced expression of both HIV co-receptors, CCR5 and CXCR4, was detected [139]. Thus, modulation of chemokine receptor expression on $CD4^+$ T lymphocytes likely represents one mechanism by which GBV-C co-infection influences HIV disease progression.

Directly inhibiting HIV-1 entry

Several groups have proposed that the GBV-C E2 protein modifies HIV disease progression [42]. GBV-C E2 protein inhibits HIV entry when added to $CD4^+$ cells [140]. It has been suggested that GBV-C E2 protein directly targets HIV-1 particles and blocks entry of virions [141]. Synthetic peptides of the GBV-C E2 domain have been shown to interact with the HIV-1 fusion protein and to modify its conformation [142]. This indicates a possible alteration of the interaction of HIV-1 fusion protein with the cell membrane decreasing cellular membrane fusion in a dose-dependent manner [143,144]. Furthermore, Mohr *et al.* have found that naturally occurring GBV-C E2 antibodies from HIV-negative individuals and experimentally induced GBV-C E2 antibodies neutralize HIV-1 infection *in vitro* by inhibit of HIV attachment, but do not inhibiting HIV entry following attachment [145]. Therefore, further investigations of the exact mechanism of the GBV-C E2/HIV interaction may not only lead to better understanding of the beneficial effect of GBV-C on HIV disease, but also possibly open new therapeutic strategies for HIV-1 treatment.

Modulating T-cell activation

Chronic immune activation is a characteristic of progressive HIV disease. Thus, cellular immune responses are critical in the control of viral replication [146]. Recently, a lower percentage of T lymphocytes expressing $CD38^+CD4^+$, $CD38^+CD8^+$ and $CCR5^+CD8^+$ were observed in GBV-C viremic HIV patients [147]. This effect of GBV-C viremia was independent of HIV-1 viral load or CD4/CD8 cellular status. Thus, reduced activation of $CD4^+$ and $CD8^+$ T cells in GBV-C/HIV co-infected patients may be a potential mechanism of ameliorating HIV disease.

Influencing Fas-mediated apoptosis

It is postulated that enhancement of Fas (CD95/Apo-1) expression on virus-infected cells is important in controlling infection through elimination of infected cells by apoptosis. In HIV infected individuals, the percentage of Fas expressing T and B lymphocytes is higher compared with healthy controls [148]. Fas expression on $CD4^+$ and $CD8^+$ T-cells rises with progression of HIV disease and augments Fas-mediated cell death [149]. In HIV infected patients on HAART, spontaneous and Fas-mediated apoptosis of PBMCs is reduced [150].

Moenkemeyer *et al.* found that GBV-C co-infection in HIV patients not receiving HAART was associated with a lower percentage of Fas expressing cells compared with HIV mono-infected individuals [151]. Furthermore, this effect correlated directly with Fas-mediated apoptosis after priming cells with an anti-Fas monoclonal antibody *in vitro*. Lower expression of Fas on the cell surface and reduced Fas-mediated apoptosis may contribute to the beneficial effect of GBV-C co-infection on HIV disease progression.

Conclusion

GBV-C, a member of the *Flaviviridae* family, is distributed world-wide. GBV-C shares common routes of transmission with HCV and HIV, resulting in co- and triple-infection in humans. GBV-C does not cause any human disease on its own. Nonetheless, a beneficial effect of GBV-C co-infection on HIV disease progression has raised considerable interest in this virus. Several mechanisms of interaction between GBV-C and HIV have been proposed, for example, influencing antiviral cytokine production, HIV co-receptor expression, direct inhibition of HIV-1 entry, T-cell activation and Fas-mediated apoptosis. These mechanisms warrant further study to hopefully open new ways of treatment of HIV infection in the future.

Expert commentary & five-year view

In the past years, GBV-C has shifted from the research field of viral hepatitis to HIV, as GBV-C was found not to be a pathogenic agent of hepatitis but rather a beneficial modulator of HIV infection and disease progression. Recent studies focus on the identification of mechanisms of interaction between HIV, GBV-C and the immune system.

As there are several proposed ways of interaction, different clinical applications of GBV-C in treatment of HIV infection can be envisioned.

Characterization of the immunogenic domains of the GBV-C E2 protein responsible for inducing E2 antibodies and/or inhibiting HIV-1 entry may facilitate development of novel HIV-1 vaccines for the treatment and prevention of HIV disease.

Furthermore, GBV-C E2-derived peptides have been demonstrated to interact with HIV-1 cell fusion by directly inhibiting HIV-1. Thus, synthetic GBV-C peptides may open the way to the design of new therapeutic drugs for HIV.

Finally, deep understanding of the GBV-C-induced modulation of the immune system may provide further access to new therapeutic strategies of HIV infection.

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Key issues

- GB virus C (GBV-C) is a member of the *Flaviviridae* family and closely related to HCV.
- However, GBV-C replicates in lymphocytes rather than in hepatocytes.
- No human disease has been associated with GBV-C infection.
- Epidemiological studies have described an association between GBV-C co-infection and decreased morbidity and mortality in HIV-infected individuals.
- Several mechanisms of interaction between GBV-C and HIV have been proposed, including altered cytokine profile, HIV co-receptor expression, T-cell activation, Fas-mediated apoptosis and direct inhibition of HIV replication.
- Further understanding of the GBV-C/HIV interactions may lead to new therapeutic drugs and novel treatment strategies in HIV.

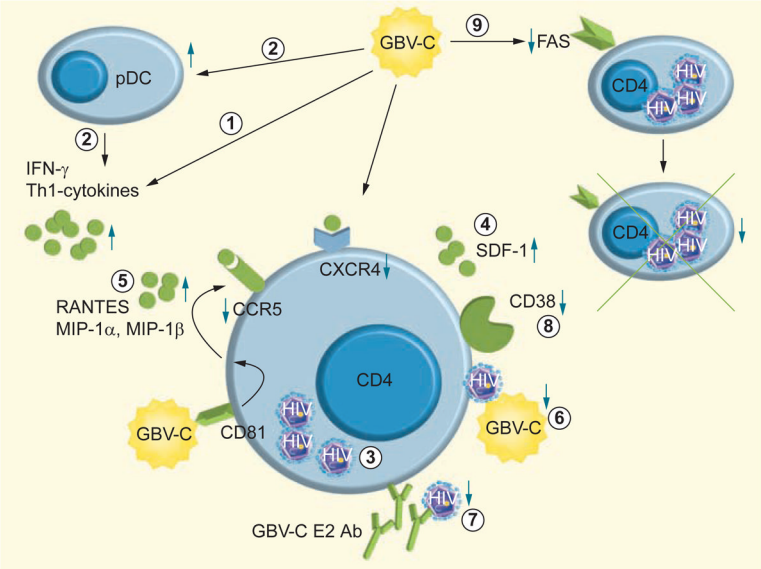

Figure 1. Proposed molecular interactions of GB virus C with HIV

(1) GBV-C alters the cytokine profile during HIV -infection, thereby stabilizing Th1 cytokine expression [127,128]. **(2)** A major source of Th1 cytokines are circulating $CD80^+$ pDCs, which are increased in GBV-C co-infection [129]. **(3)** HIV replication is also inhibited by GBV-C proteins [87,132]. **(4)** GBV-C NS5A phosphoprotein induces SDF-1 release, thereby decreasing CXCR4, an important co-receptor of HIV [133–135]. **(5)** Furthermore, secretion of RANTES, MIP-1α and MIP-1β – natural ligands of the other HIV co-receptor CCR5 – is elevated during GBV-C co-infection leading to lower surface expression of CCR5 [131,137]. **(6)** Direct inhibition of HIV entry by GBV-C E2 protein has been proposed and interaction of GBV-C E2 with the HIV-1 fusion protein has been shown [141–144]. **(7)** Furthermore, GBV-C E2 Abs have been demonstrated to neutralize HIV-1 infection by inhibition of viral attachment [145]. **(8)** GBV-C alters T-cell activation leading to a lower percentage of T lymphocytes expressing CD38 [147]. **(9)** Finally, GBV-C co-infection leads to lower Fas expression on T and B lymphocytes, thereby reducing Fas-mediated apoptosis [151].

Ab: Antibody; CCR: Chemokine receptor; GBV-C: GB virus C; pDC: Plasmocytoid dendritic cell; RANTES: Regulated on activation, normal T-cell expressed and secreted; SDF-1: Stroma- derived factor-1.