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Research Article www.enlivenarchive.org *Enliven: Journal of Genetic, Molecular and Cellular Biology*

ISSN: 2379-5700

Evolving Research in the Relationship Between Beta2-Glycoprotein I and Liver Diseases

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Received Date: 17th March 2015
Accepted Date: 01st April 2015
Published Date: 06th April 2015

Citation: Jing X, Chen WX, Tian ZB, Kong XJ, Ding XL (2015) Evolving Research in the Relationship Between Beta2-Glycoprotein I and Liver Diseases. Enliven: J Genet Mol Cell Biol 2(1): 001.

Abstract

Beta2-glycoprotein I (β_2GPI) is a highly abundant glycoprotein in plasma. To date, most studies have focused on the relationship between β_2GPI and antiphospholipid antibody syndrome (APS). Recent clinical trials indicated that the expression of and antibody titers against β_2GPI are altered in various liver diseases. This article outlines the role of β_2GPI and anti-β_2GPI antibodies in liver diseases.

Keywords: Beta2-glycoprotein I (β_2GPI); Liver diseases

Introduction

Beta2-glycoprotein I (β_2GPI) is a glycoprotein that is synthesized in the liver and is highly abundant in plasma. In the last decade, studies have shown that β_2GPI is a major target antigen in antiphospholipid antibody syndrome (also named as antiphospholipid syndrome, APS), and that anti-β_2GPI antibodies form a major proportion of the antiphospholipid antibodies [1]. The detection of anti-β_2GPI antibodies has been included in the clinical diagnostic criteria for APS since 2006 [1]. Since the discovery of β_2GPI as a major antigen in APS, the relationship between β_2GPI and autoimmune diseases in general has received great attention. The liver is an important organ in the immune system, and its pathology is typically associated with an immunological component. Recent clinical trials indicated that the expressions of β_2GPI and anti-β_2GPI antibody titers were altered in various liver diseases. This study outlines the roles of β_2GPI and anti-β_2GPI antibodies in liver diseases.

Chronic Hepatitis

The viral infection of liver cells triggers an immune response via different mechanisms. Anti-cardiolipin (aCL) antibodies are often present in various viral infections, including hepatitis A, B, and C. Autoimmune hepatitis is manifested clinically to different degrees. Therefore, studies have assessed the role of β_2GPI in chronic hepatitis.

Hepatitis C Virus (HCV) Infection

Antiphospholipid antibodies have been reported in HCV carriers [2]. The individuals chronically infected with hepatitis C virus present a significant production of antiphospholipid antibodies, mainly IgA anti-β_2GPI antibodies, which are not associated with clinical manifestations of antiphospholipid syndrome [2]. Although anticardiolipin antibodies and/or anti-β_2GPI antibodies were detected in an HCV-infected population with APS clinical manifestations, aCL antibodies are an epiphenomenon in HCV patients, with no obvious clinical or laboratorial significance [2,3]. In contrast, some studies showed that aCL antibodies and anti-β_2GPI antibodies were associated with HCV, and that they might play role in the infection [4,5]. The correlation between HCV and APS or anti-β_2GPI antibodies remains controversial. However, an increased protein level of β_2GPI was found in the serum of patients with hepatic fibrosis after HCV infection, suggesting that β_2GPI protein might be a biological indicator of hepatic fibrosis [6].

Hepatitis B Virus (HBV) Infection

Five sets of experiments showed that anti-β_2GPI antibodies were present in <10% of HBV-infected patients [7]. In addition, there was no clinical correlation between APA or anti-β_2GPI antibodies and APS after HBV infection. Nevertheless, both aCL antibodies and anti-β_2GPI antibodies can be present in the HBV-infected patients for more than 12 weeks [8].

Some reports have investigated whether β_2GPI is a receptor for HBV-infected liver cells. In 1994, Mehdi et al. [9] obtained purified liver cell membranes from normal liver tissue, and discovered that β_2GPI protein bound to radionuclide probe-labeled recombinant hepatitis B surface antigens (HBsAg, only containing small S proteins). β_2GPI protein also bound directly to HBsAg isolated from plasma. This binding was saturable, and could be blocked by an excess of recombinant HBsAg, hepatitis B surface antibodies (HBsAb), and anti-β_2GPI antibodies [9]. Lipoproteins are necessary for the binding between β_2GPI and HBsAg. Delipidated HBsAg and β_2GPI cannot bind, whereas the presence of phospholipids restores the binding ability [10]. During normal lipid transport, the degradation of chylomicrons (CM) and high-density lipoproteins (HDL) occurs mainly in hepatic cells, suggesting that HBV might associate with CM or HDL to enter hepatic cells. After a conformational change, β_2GPI binds to HBsAg more efficiently, suggesting that one or several lysine sites on β_2GPI might be involved in this binding [11].

Despite the binding between β_2GPI and HBsAg, Stefas et al. [12] found that β_2GPI could capture almost all crumbled Dane particles in the sera of HBV-infected patients. This binding was specific, and was stronger when the amount of virus increased during acute viral infection [12]. β_2GPI binds strongly to the pre-S1 region of myristylated HBV. After forming β_2GPI-HBV complexes, HBV is more likely to be recognized by antibodies, resulting in a more effective immune response for pathogen clearance [13]. HBV binds to the fifth domain of β_2GPI, which is similar to the site that binds to negative phospholipids [14].

Gao et al. used recombinant HBsAg plasmid and β_2GP to perform enzyme-linked immunosorbent assay (ELISA) to analyze their relationship, and the results were consistent with previous reports by Mehdi et al. [14-16]. In addition, they detected a liver cell surface protein that bound to β_2GP, and later identified that protein as annexin II [17,18]. Annexin II is not a transmembrane protein, and cannot mediate downstream signal transduction. Studies revealed that annexin II binds to Toll-like receptors (TLRs) to mediate innate immunity and initiate protective immune responses. Their levels of anti-β_2GPI antibodies of patients with chronic hepatitis B and post-hepatitis B cirrhosis were higher than those found in normal control individuals. In addition, the levels of anti-β_2GPI antibodies were higher in patients with post-hepatitis B cirrhosis than in those with chronic hepatitis B, which might be associated with liver cirrhosis [19,20]. After HBV infection, anti-β_2GPI antibodies are present in patient serum. Gao et al. [19] hypothesized that HBV uses β_2GPI and liposomes to enter liver cells and trigger an autoimmune response; however, an additional mechanism was also proposed: molecular mimicry. Blank et al. suggested that viral or bacterial infections might trigger the production of anti-β_2GPI antibodies via molecular mimicry [21]. It is possible that certain pathogens with a similar molecular structure as β_2GPI might be presented to T cells by B cells, macrophages, and dendritic cells together with human leukocyte antigen factor, which stimulates plasma cells to secrete anti-β_2GPI antibodies. The three-hexapeptide structure of β_2GPI was identified the pathogen-specific recognition site for anti-β_2GPI antibodies. It also activates endothelial cells and induces APS under experimental conditions. In these hexapeptides structure, TLRVYK polypeptide locates in the third domain of β_2GPI molecule and shares the homology with many pathogens [21]. Therefore, it is necessary to assess whether molecular mimicry occurs during HCV or HBV infection.

Alcoholic Liver Disease

The immune response also plays a role in excessive alcohol consumption-induced alcoholic liver disease. Liver cell damage is a critical event in alcoholic liver disease. Beta2-GPI, as a cofactor of autoantibodies binding phospholipids (e.g., antiphospholipid antibody), has an indirect relationship with alcoholic liver disease. Antiphospholipid antibodies and ethanol are detected in patients with alcoholic liver disease, and are closely related to oxidative damage. Their functional target is the epitope formed by the interaction between β_2GPI and oxidized phospholipids [22]. Perney et al. showed that antiphospholipid antibody (including anti-β_2GPI antibodies) titers correlate with degree of injury in the liver histology of alcoholic liver disease, but was not associated with ethanol uptake [23].

Autoimmune Liver Diseases

Autoimmune liver diseases mainly include autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC). A major characteristic of autoimmune liver diseases is the detection of various specific or non-specific autoantibodies. Studies assessing the involvement of β_2GPI in autoimmune liver diseases are still at their initial stage, and so are not extensive. Beta2-GPI relies mostly on antiphospholipid antibodies (i.e., anti-β_2GPI antibodies) or cofactor-produced autoantibodies to exert its functions. A recent study demonstrated that the detection rate of IgM anti- β_2GPI antibodies was higher in patients with AIH compared with PBC. However, this study did not report the effect of the different antibody prevalence on either liver disease [24]. A study by Gabeta et al. reported that the prevalence of IgA anti- β_2GPI antibodies was high in AIH patients (50.8%), and that it was associated with disease severity and biochemical markers in both AIH and PBC patients [25]. Beta2-GPI is the most common autoantigen in autoimmune liver diseases, and the prevalence of anti-β_2GPI antibodies is higher than in these conditions compared with other liver diseases.

Hepatic Cirrhosis and Liver Cancer

Beta2-GPI is one of the most abundant plasma proteins, and is synthesized mainly in the liver. In 1994, Quintarelli et al. detected anti-cardiolipin antibodies in patients with hepatic cirrhosis, and then assessed whether β_2GPI plays a role in hepatic cirrhosis. They measured β_2GPI levels in 63 blood samples from patients with hepatic cirrhosis, and found that β_2GPI levels were significantly lower in patients with severe liver failure than in those with moderate hepatic impairment [26]. Gries et al. recently performed a study in 103 patients with hepatic cirrhosis caused by HBV, HCV, alcohol, or hemochromatosis. They found positive correlations between β_2GPI protein levels and markers of liver protein synthesis function (e.g., albumin, cholinesterase, and length of time taken for blood to coagulate). However, β_2GPI protein levels were negatively correlated with bilirubin, the aspartate transaminase/alanine transaminase (AST/ALT) ratio, and C-reactive protein, suggesting that β_2GPI protein levels were reduced in patients with chronic liver diseases. In addition, β_2GPI protein levels decline with an increasing disease severity [27]. Patients with liver cirrhosis and portal vein thrombosis have no significant expression of anti-β_2GPI antibodies, whereas those with portal vein thrombosis alone express detectable levels [28].

A study of Asian cancer patients by Yoon et al. showed that 60.9% of patients with cancer-associated thrombosis had antiphospholipid (aPL) antibodies. Anti-β_2GPI antibodies were the most dominant antiphospholipid antibodies (46.9%). IgA anti-β_2GPI antibodies were associated with stroke, large-scale recurrent venous thromboembolism, and arteriovenous thrombosis. These results suggest that the presence of antiphospholipid antibodies, particularly IgA anti-β_2GPI antibodies, is associated with a high-risk of thrombosis and related diseases in cancer patients [29]. An in vitro study demonstrated that the expression of β_2GPI was increased in hepatocellular carcinoma cells after hepatitis B infection. In addition, β_2GPI protein and HBsAG activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), suggesting that β_2GPI might be involved in the pathogenesis of liver cancer after hepatitis B infection [30].

Questions and Prospects

Beta2-GPI is abundant in plasma, and has diverse physiological functions. It is the most representative antigen of autoimmune diseases, and is involved in several such conditions. Beta2-GPI is also an autoimmune antigen in liver disease. However, its functions remain unclear. For example, It is controversial whether the presence of anti-β_2GPI antibodies in some liver diseases is relevant for disease occurrence and development. In addition, it is unclear if the association between β_2GPI and HBsAg in HBV-infected liver cells plays a role as an HBV receptor, or if it functions as a bridge during the binding of HBV to liver cells. Finally, It is unknown if β_2GPI can be used as a diagnostic factor or as a marker for liver disease severity. These questions should be addressed in future studies. The relationship between β_2GPI and liver diseases should also be assessed further. Finally, experiments should be performed to elucidate the pathogenesis of liver diseases and identify possible treatment options.

Acknowledgments

This work was supported by the National Natural Science Youth Foundation of China (No. 81101853). Tian Qing liver disease Foundation of Chinese Hepatitis Prevention and Control Research Fund (TQGB20120076).

Conflict of Interest Statement

The authors declare that they have no competing interests.

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