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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Exploring the Complex Role of Coagulation Factor VIII in Chronic Liver Disease

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SUMMARY

Coagulopathy and chronic liver diseases are closely interconnected. In this review article we provide evidences of the role of procoagulant Factor VIII in chronic liver disease.

Chronic liver disease is one of the leading causes of death in the United States. Coagulopathy is often a sequela of chronic liver disease, however, the role and regulation of coagulation components in chronic liver injury remain poorly understood. Clinical and experimental evidence indicate that misexpression of the procoagulant factor VIII (FVIII) is associated with chronic liver disease. Nevertheless, the molecular mechanism of FVIII-induced chronic liver injury progression remains unknown. This review provides evidence supporting a pathologic role for FVIII in the development of chronic liver disease using both experimental and clinical models. *(Cell Mol Gastroenterol Hepatol 2021;12:1061–1072; https://doi.org/10.1016/j.jcmgh.2021.02.014)*

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Chronic liver disease (CLD) is among the leading causes of death in the United States.[1] CLD also is responsible for approximately 70% of the total number of liver transplants every year.[2] In most forms of CLD, progressive injury damages the liver parenchyma leading to inflammation, vascular remodeling, fibrosis, and angiogenesis.[3–6] Without effective treatment, CLD can lead to end-stage liver disease and liver failure, which contributes to nearly 1 million deaths per year worldwide.[7]

Coagulopathy is often a sequela of CLD because the liver damage causes impaired coagulation.[8,9] With the exception of von Willebrand factor (VWF), all other coagulation-related proteins (Factor I, II, V, VIII, IX, X, XI, XII, and XIII, and tissue factor) are synthesized in the liver[9] and, thus, both acute and chronic liver failure may impair the synthesis of coagulation factors.[10,11] The onset of cirrhosis complications such as variceal bleeding, portal hypertension, or infection/sepsis also may impair the coagulation cascade further.[12,13] Moreover, clinical studies in cirrhosis patients and experimental studies in mouse models of CLD have suggested that perturbation of the coagulation cascade promotes acute liver toxicity and CLD.[9,10,14–17] Thus, the association of liver injury with coagulation extends beyond the impact of liver disease on the synthesis of coagulation factors to include a role for coagulation factor activity in the initiation and progression of CLD.

End-stage CLD frequently is associated with clinical bleeding and decreased levels of most procoagulant factors, with the notable exceptions of Factor VIII (FVIII) and VWF, which are increased (until late in the disease).[10] Emerging evidence suggests that FVIII is a critical mediator of coagulation in CLD.[10,11] In this review, we aim to provide a balanced view of the roles of FVIII in CLD based on studies in both mice and human beings. In addition, we briefly address the potential therapeutic implications of these results and describe the potential challenges and knowledge gaps to be addressed by future studies.

Hepatic Synthesis, Secretion, and Clearance of FVIII

FVIII is a plasma glycoprotein that is synthesized primarily in the liver.[18] Although a few studies have shown the contribution of hepatocytes in FVIII synthesis,[18–21] liver sinusoidal endothelial cells are the predominant site of FVIII synthesis.[18,22–30] Among other organs, lung,[31] spleen,[32,33] and lymphatic tissues[34] also have been implicated to produce FVIII. Despite the fact that the identity of FVIII-secreting cells was a long-standing debate in the past, liver sinusoidal endothelial cells now are considered the chief source for the level of circulating FVIII.

Immunohistochemical staining of FVIII in the liver has confirmed its presence in the vessels around the intrahepatic large bile ducts (peribiliary vascular plexus) (Figure 1*A*). Factor VIII is synthesized as a 330-kilodalton single-

Abbreviations used in this paper: **CLD, chronic liver disease; ER, endoplasmic reticulum; FHF, fulminant hepatic failure; FVIII, Factor VIII; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LMAN1, Lectin, Mannose Binding 1; mRNA, messenger RNA; NAFLD, nonalcoholic fatty liver disease; NO, nitric oxide; VWF, von Willebrand factor.**

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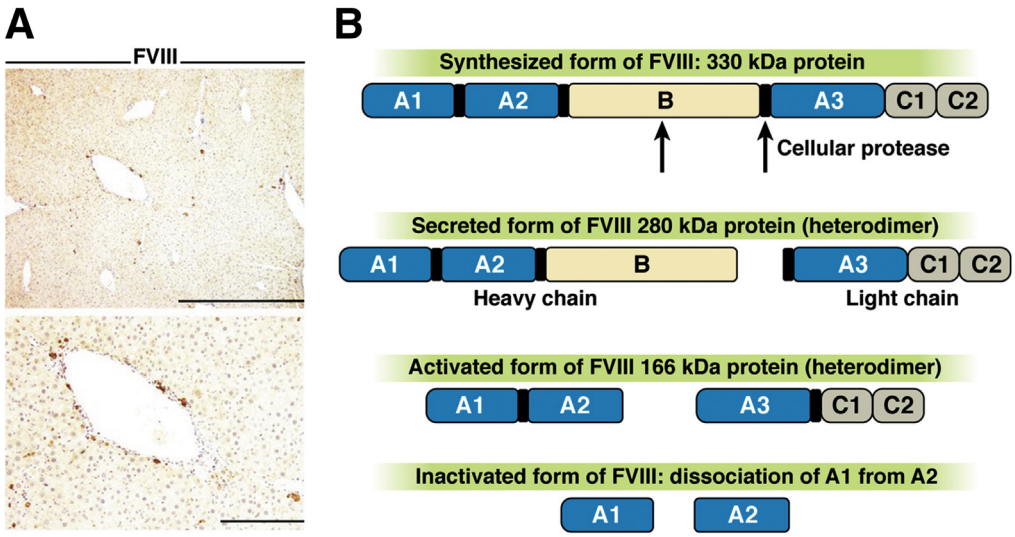

Figure 1. FVIII is synthesized in hepatic sinusoidal endothelial cells. (*A*) Immunohistochemical staining of FVIII in wild-type liver shows its localization in the liver. (*B*) Schematic showing the structure of FVIII protein and its different cleaved forms.

polypeptide chain with a domain structure (A1-A2-B-A3-C1-C2) that circulates in the plasma as a heterodimeric protein consisting of a metal ion-linked light chain and heavy chain[35] (Figure 1*B*). The heavy chain (90–220 kilodaltons) contains the A1-A2-B domains and is heterogenous as a result of limited proteolysis within the B domain. The light chain (80 kilodaltons) consists of the A3-C1-C2 domains.

Upon synthesis, mature FVIII polypeptide translocates to the lumen of the endoplasmic reticulum (ER) for glycosylation. Within the ER, FVIII interacts with a number of chaperone proteins, including calreticulin, calnexin, and the IgG-binding protein,[36–38] which causes FVIII retention in the ER. Moreover, FVIII is prone to protein misfolding, which altogether results in its low level of expression at the cellular level.[39,40] Unfolded FVIII accumulates in the ER lumen and activates ER stress-response genes, leading to oxidative stress and apoptosis.[39] Antioxidants have been shown to improve FVIII secretion and thus prevent ER stress–induced oxidative damage and apoptosis.[41] Analysis of secreted FVIII into the plasma has shown that ER protein Ire1α regulates the secretion efficiency of FVIII.[39] Loss of Inositol-requiring transmembrane kinase/endoribonuclease 1α (IRE1α) has been linked to chronic liver injury,[42] suggesting a potential link of misfolded FVIII protein in CLD.

FVIII trafficking from ER to the Golgi complex is facilitated through interaction with the Lectin, Mannose Binding 1 (LMAN1)/Multiple Coagulation Factor Deficiency 2, ER Cargo Receptor Complex Subunit (MCFD2) complex.[43] Mice lacking LMAN1 have completely blocked FVIII secretion.[23] Secreted FVIII is associated with VWF in the sinusoids and circulates in the bloodstream in an inactive form.[44] VWF stabilizes the structure of FVIII, prevents the nonspecific binding of FVIII to platelets and endothelial cells, and acts as a cofactor for thrombin-catalyzed cleavage of the FVIII light chain.[45] For a complete description of FVIII structure and its interaction with VWF, readers are referred to the studies by Chavin,[46] Vehar et al,[47] and Fay.[48]

Upon injury to the blood vessels, FVIII is activated and separates from VWF, which permits FVIII interaction with platelets.[49] Activated FVIII interacts with coagulation factor IX, which promotes a chain of additional chemical reactions that form a blood clot.[50] Activated protein C and Factor Xa (FXa) also are known to deactivate FVIII.[51] For a detailed role of FVIII in coagulation, readers are referred to the studies by Chavin,[46] Lenting et al,[52] and Mazurkiewicz-Pisarek et al.[53]

The endocytic trafficking and clearance of FVIII recently has gained much attention.[54–56] The removal of FVIII from the bloodstream requires the presence of specialized clearance receptors. Low-density lipoprotein receptor–related protein is considered one of the chief FVIII clearance receptors that localizes to the hepatocyte membrane.[55] The endothelial lectin C-Type Lectin Domain Family 4 Member M (CLEC4M) also is shown to regulate FVIII clearance in both a VWF-dependent and -independent manner.[57,58] CLEC4M binds to FVIII and promotes its internalization via clathrin-coated pit, followed by endosomal trafficking and lysosomal degradation of FVIII.[59,60] Similarly, stabilin-2, a scavenger receptor expressed on the sinusoidal endothelial cells of the liver, spleen, and lymphatics, functions as a clearance receptor of FVIII. Although the interaction of VWF–FVIII and stabilin-2 was identified through genetic wide association study (GWAS),[61] the stabilin-2–deficient murine model showed mechanistic details of stabilin 2–FVIII–VWF interaction by regulation of the half-life of VWF–FVIII and the immune response to VWF–FVIII concentrates.[62] Among other factors, a number of hepatocyte- and macrophage-expressed asialoglycoprotein receptors such as Sialic Acid Binding Ig Like Lectin 5 (SIGLEC5) and teroid Receptor RNA Activator 1 (SR-A1) also have been reported to promote FVIII clearence.[63,64] Thus, the liver plays a predominant role in FVIII synthesis, trafficking, and degradation as shown in Figure 2.

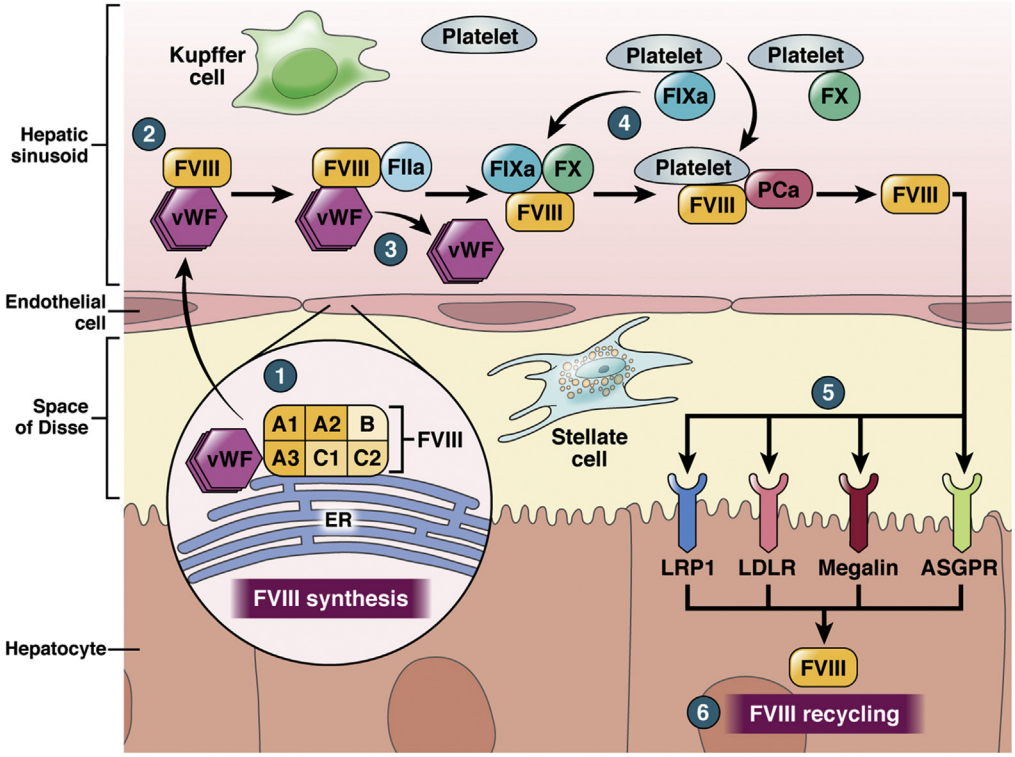

Figure 2. Hepatic synthesis, secretion, and clearance of FVIII. (*A*) Schematic diagram showing the synthesis, secretion, trafficking, and degradation of FVIII in the liver. Upon its synthesis in the sinusoidal endothelial cells, FVIII associates with VWF. Upon its activation, FVIII gets cleaved and dissociated from VWF. Activated FVIII interacts with Factor IX and platelets and promotes a blood clot formation. The removal of FVIII from the bloodstream is promoted by a specialized clearance receptor low-density lipoprotein-receptor–related protein (LRP) that localizes to the hepatocyte membrane. ASGPR, Asialoglycoprotein receptor; FIXa, Factor IXa; FX, Factor X; LDLR, Low Density Lipoprotein Receptor; PCa, protein C.

Relevance of FVIII in CLD

Factor VIII and Portal Hypertension

Portal hypertension is defined as the pathologic increase in hepatic sinusoidal pressure, which causes increased intrahepatic resistance to portal blood flow and an increase in hepatic venous pressure gradient (<10–12 mm Hg).[65] Several clinical studies have confirmed that the plasma FVIII level increases during portal hypertension.[66–68] Cirrhosis is considered one of the predominant causes of portal hypertension.[69] Portal hypertension–related variceal bleeding is a typical finding in cirrhosis that frequently is associated with increased FVIII in the serum of patients with moderate varices.[70]

Blockage of blood flow or the presence of a blood clot in the portal vein can cause portal hypertension.[71] FVIII levels are significantly higher in patients with primary extrahepatic portal vein obstruction,[66] even in the absence of cirrhosis. Higher levels of FVIII also are associated with an increased risk for deep vein thrombosis[66] and thrombophilia-induced idiopathic extrahepatic portal vein obstruction with portal hypertension.[55] In addition, a high level of FVIII is considered a risk factor for portal vein thrombosis in patients with CLD, and in children with extrahepatic portal vein obstruction secondary to CLD.[68] In mice undergoing partial portal vein ligation, a widely used model of portal hypertension,[72] plasma FVIII levels are significantly higher than in sham-operated murine controls.[72]

Although the molecular mechanism of FVIII increase in portal hypertension remains unknown, there are several hypotheses for changes in FVIII levels in portal hypertension. Dysfunctional sinusoidal endothelial cells (the source of FVIII) may contribute to the extrahepatic increase in FVIII levels during portal hypertension.[72] Another reason for FVIII increases in portal hypertension is a reduction in nitric oxide (NO) levels.[73] Loss of NO/endothelial NO synthase activity is associated with increased hepatic resistance, dysfunctional sinusoidal endothelial cells, portal vein thrombosis, and subsequent development of portal hypertension.[74,75] Several studies have shown that NO negatively regulates FVIII and VWF expression.[76,77] In cirrhotic conditions, NO activity is reduced, leading to increased intrahepatic vascular resistance.[76,77] Figure 3 shows the schematic of FVIII in portal hypertension.

Factor VIII and Cirrhosis

Cirrhosis is characterized by persistent fibrosis and nodule formation leading to alteration of the normal lobular organization of the liver.[78] Cirrhosis is one of the frequent clinical outcomes in all CLD (including viral infections,

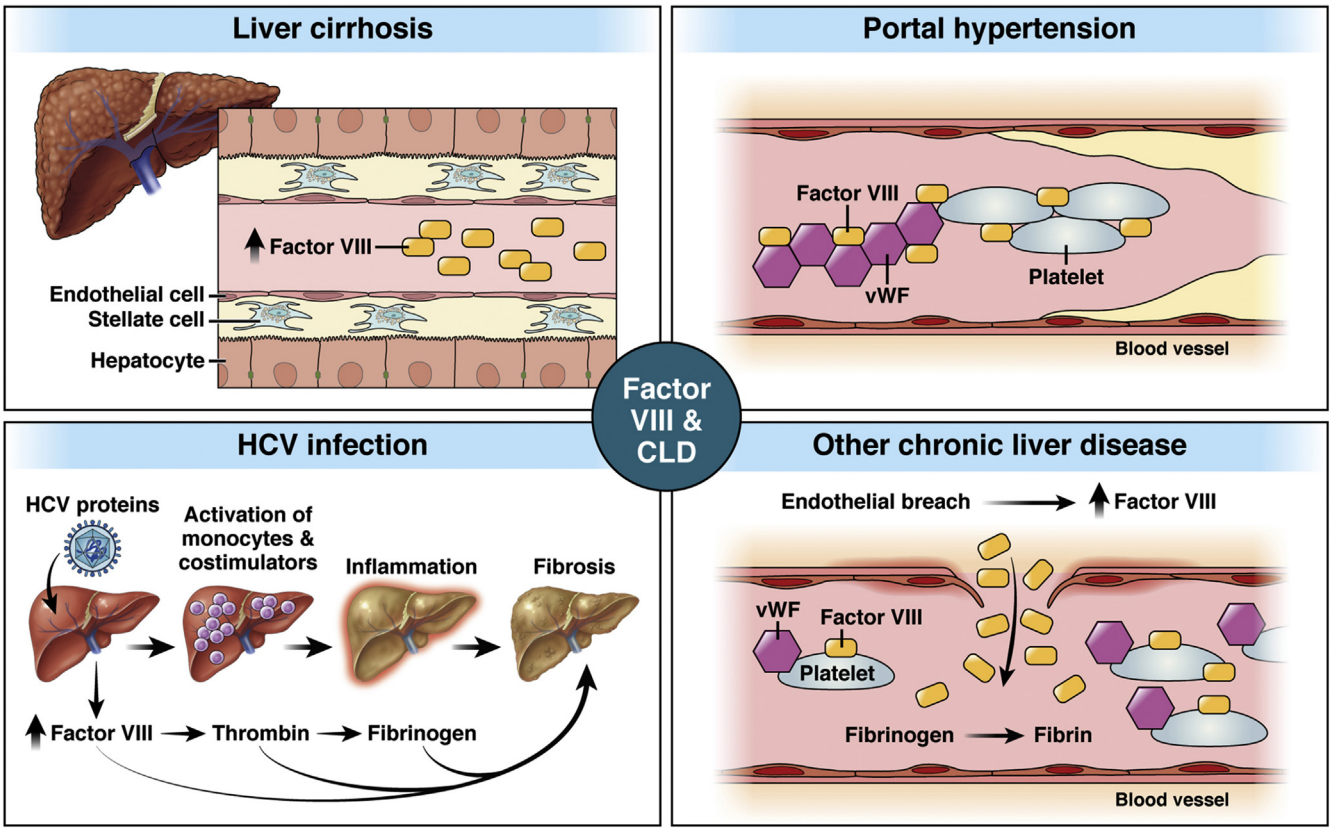

Figure 3. The multifaceted role of factor VIII in chronic liver injury. (*A*) Schematic diagram showing the role of FVIII in various chronic liver disease models. In cirrhosis, the protein level of FVIII is increased in the plasma during advanced stages. In hepatitis C, FVIII expression is inhibited, leading to accumulation of fibrinogen and associated injury. In portal hypertension, FVIII increasingly is found to be increased and to form a complex with VWF in the plasma. In all other CLD models, an endothelial breach resulting from injury is associated with misexpression of FVIII in both liver and plasma.

toxins, hereditary conditions, or autoimmune processes).[65] Numerous clinical reports have confirmed a significant increase in plasma FVIII levels in cirrhotic patients, specifically during the advanced/late stages of cirrhosis.[79–84]

Although the exact reason for FVIII increase in cirrhosis is not known, there are several hypotheses for how FVIII levels are changed during cirrhosis. Cytokine release from the necrotic tissue of cirrhotic livers can lead to increased FVIII synthesis.[11,12] Extrahepatic sites of FVIII synthesis[85–87] (the spleen, kidney, lungs, and endothelium) also are speculated to be the cause of increased FVIII synthesis. Other possible causes of increased FVIII levels include abnormal protein production by the endothelium, misfolding of FVIII that interfere with its secretion,[88] impaired catabolism of normal proteins,[39] and factors regulating FVIII including increased hepatic VWF biosynthesis or decreased low-density lipoprotein receptor–related protein expression or protein C deficiency.[80,89]

An increase in FVIII expression can occur as a result of impaired clearance of hemostatic complexes during advanced stages of cirrhosis.[81] Among other factors, lipopolysaccharide[90] recently was shown to be a potential trigger of FVIII release.[75] Interestingly, despite a significant increase in protein level, the messenger RNA (mRNA) level of FVIII was reduced in these patients, suggesting a post-translational increase of the FVIII protein level in cirrhosis.[91,92]

Because cirrhotic patients frequently show higher FVIII, VWF antigen, and a FVIII-to–protein C ratio, FVIII has a significant potential to be used as a biomarker to independently predict new onset of ascites, variceal bleeding, and mortality in cirrhotic patients.[79] Figure 3 shows the schematic of FVIII in liver cirrhosis.

Factor VIII and Hepatitis C

The hepatitis C virus (HCV) is a primary global health concern, with approximately 71 million chronically infected people.[93] HCV infection can increase the risk of developing end-stage CLD and hepatocellular carcinoma (HCC).[94] FVIII deficiency (hemophilia A) has been associated with HCV infections,[95] predominantly resulting from exposure to virally contaminated blood. Patients with hemophilia infected with human immunodeficiency virus (HIV) and HCV after treatment with a contaminated FVIII concentrate frequently developed cirrhosis and HCC.[96,97]

Although HCV infection is not known to induce the development of FVIII inhibitors,[98] some patients with HCV–HIV co-infection showed decreased FVIII levels

Table 1. Evidence in Support of a Role of FVIII in Chronic Liver Disease With Potential Mechanisms Involved

Disease	Clinical evidence	Experimental evidence	Potential mechanisms
Cirrhosis	↑ Plasma FVIII levels in cirrhotic patients[79–84] ↓ Hepatic FVIII mRNA level of FVIII during cirrhosis[91,92] ↑ Plasma FVIII levels in cirrhosis without portal vein thrombosis[81] ↓ Plasma FVIII levels cirrhotic with portal vein thrombosis[81]		Compromised clearance of hemostatic complexes[81] Cytokine release from the necrotic tissue of cirrhotic liver[11,12] Extrahepatic sites of FVIII synthesis[85–87] Abnormal protein production/ misfolding of FVIII[88] and impaired catabolism[39] LPS induced FVIII release[75] Increased hepatic VWF biosynthesis or decreased level of LRP/protein C[80,89]
Portal hypertension	↑ Plasma FVIII levels in primary extrahepatic portal vein obstruction[66] ↑ Plasma FVIII levels in thrombophilia-induced IEPVO, with portal hypertension[55] ↑ Plasma FVIII in levels in PVT patients with CLD[123] ↑ Plasma FVIII levels Children with extrahepatic portal vein obstruction[68]	↑ FVIII levels followed by portal vein ligation in murine models[68]	Impaired function of sinusoidal endothelial cells[74,75] Reduction in NO level[76,77]
Hepatitis C	↓ Plasma FVIII levels[95]		Development of human FVIII inhibitor[95] Hemophilia patients infected with HIV[124,125]
Acute liver failure Acetaminophen-induced liver failure Drug-induced liver failure FHF	↑ Plasma FVIII level[112,113] ↓ Plasma FVIII[103] ↓ Plasma FVIII has been associated with thioxanthenes,[103] interferon,[95] and fludarabine[103] ↑ Plasma FVIII level[102]	A study performed in pigs showed that acetaminophen overdose leads to ↓ FVIII[70]	Inhibitor formation[99]
Other chronic liver injury models: Alcoholic cirrhosis NAFLD	↑ FVIII in the sinusoidal cells[106,107] ↑ FVIII level[111]	FVIII-deficient mice on a high-fat diet developed NAFLD phenotypes[122]	
Hepatic fibrosis	↑ FVIII level associated with liver fibrosis17 Hemophilia patients with chronic HCV infection showed reduced rate of fibrosis or liver disease progression73 FVIII-related antigen was found in the capillaries adjoining the pericellular fibrotic region[100]		Tissue ischemia, parenchymal extinction, and direct thrombin-mediated stellate cell activation via PAR-1 cleavage17 Coagulation cascade activity by activation of the hepatic stellate cells[101] The structural and immunohistochemical changes of sinusoidal endothelial cells74
Liver surgery	↑ Plasma FVIII level during the intraoperative and early postoperative period[41,43] ↑ FVIII level in patients undergoing liver transplant[41,43,87] ↑ FVIII level in children undergoing liver transplant[117]		

Table 1. Continued

Disease	Clinical evidence	Experimental evidence	Potential mechanisms
Liver regeneration	↑ FVIII plasma level[92] ↓ FVIII mRNA expression in the liver[92]		Delay in the inactivation of plasma FVIII caused by increased VWF in plasma or decreased FVIII clearance in the liver[92] Alteration of the intracellular trafficking pathway of FVIII and its rapid release from the storage sites after partial hepatectomy[92]

IEPVO, idiopathic extrahepatic portal vein obstruction; LPS, lipopolysaccharide; LRP, low-density lipoprotein receptor-related protein; PAR-1, protease activated receptor 1; PVT, portal vein thrombosis.

associated with the presence of a FVIII inhibitor[95] when treated with interferon-α for hepatitis C.[99] However, future research is needed to understand the mechanistic detail of inhibitor formation in viral hepatitis.

Acquired FVIII inhibitors (autoantibodies) are one of the most prominent autoantibodies that influence the clotting cascade.[99] Although the development of inhibitors against FVIII has been observed in patients with HCV infection,[95] whether FVIII inhibitor formation leads to progression or onset of acute and chronic hepatitis C is unknown. Future research consisting of both experimental and clinical studies is needed to better characterize the role of FVIII in hepatitis C pathogenesis, disease associations, and optimal disease management. Regardless of past HCV exposure, the current risk is essentially nonexistent with current FVIII products and FVIII replacement therapy is encouraged to prevent or treat bleeding.

Factor VIII and Fibrosis

Fibrosis refers to accumulation of scar tissue in the liver, which, if left untreated, can lead to cirrhosis and HCC.[4] The coagulation cascade has been shown to influence fibrosis.[15] Several studies have confirmed that hepatic inflammation and fibrosis are associated with increased expression of FVIII.[15] Immunohistochemically, FVIII-related antigen, which was not observed in the healthy sinusoidal endothelial cells, was found to be localized in the capillaries within the pericellular fibrotic region.[91] These results suggest that progression of fibrosis to cirrhosis is associated with the change in structural and immunohistochemical characteristics of the sinusoidal endothelial cells.[100]

Patients with hemophilia and chronic HCV infection show an increased rate of fibrosis progression with a Meta-analysis of Histological Data in Viral Hepatitis (Metavir) score of $\geq$3 on a transjugular liver biopsy specimen.[101] Along with FVIII, increased α-fetoprotein levels, increasing age, and past HCV treatment are risk factors in the pathogenesis of liver fibrosis.[101] Although the mechanism of altered coagulation in fibrosis remains unknown, it is hypothesized that tissue ischemia, parenchymal extinction, and direct thrombin-mediated stellate cell activation via protease activated receptor 1 (PAR-1) causes changes in the coagulation cascade, including FVIII activation.[15]

Factor VIII and Other Models of CLD

Misexpression of FVIII also has been associated with other models of CLD such as drug-induced hepatic failure, alcoholic and nonalcoholic liver diseases, and HCC. Fulminant hepatic failure (FHF) in human beings is known to cause a dramatic decrease in most hemostatic proteins, except FVIII, which shows a significant increase at the onset of the disease.[102] One of the causes of FHF is acetaminophen overdose. However, when mice were treated with acetaminophen to produce FHF, contrary to the observation in human FHF, these mice manifested markedly reduced FVIII activity along with liver injury and death.[103,104] A similar study performed in pigs also showed that acetaminophen overdose could change to a hypercoagulable state from a hypocoagulable state with a significant reduction in FVIII.[105] In these models, VWF levels were only mildly reduced, as also shown in patients, suggesting that the hypocoagulation is not owing to the loss of VWF.

Alcoholic cirrhosis is a predominant cause of liver failure and liver-related mortality. Studies have shown a significant increase in FVIII in the sinusoidal cells[106] of alcoholic cirrhosis patients, eventually leading to coagulation abnormalities.[107] Despite the consistent increase in FVIII, not much is known about its role and regulation in alcoholic cirrhosis. Stress-induced FVIII synthesis and altered characteristics of sinusoidal endothelial cells may be the potential reasons FVIII increases in ALD.[108]

Nonalcoholic fatty liver disease (NAFLD) is a common metabolic disorder with a global estimate of 25% of adults living with this disease throughout the world.[109] NAFLD progression is associated with thrombotic vascular disease and hemostatic alterations.[110] Studies also have shown that NAFLD-like conditions increase clotting factor levels in human beings, including the FVIII level as well as the VWF level,[111] both of which are known to be associated with inflammation and acute-phase reactions. However, the mechanism and effect of the FVIII increase in NAFLD disease progression are not known.

Among other CLDs, acute liver failure also has been associated with an increase of plasma FVIII level.[112,113] Table 1 summarizes the association of FVIII in CLDs from clinical studies.

Factor VIII and Liver Surgery

In liver transplantation surgeries, substantial changes in coagulation components take place.[114,115] Several studies have reported that during the intraoperative and early postoperative phase, the plasma FVIII level usually increases.[114,115] Patients with end-stage liver disease undergoing liver transplantation consistently have higher FVIII levels than patients who survived had end stage liver disease but did not undergo treatments such as liver transplantation,[116] consistent with the severity of their liver disease and criteria for transplantation based on the severity of end-stage liver disease. Studies have shown that FVIII levels also are increased in children undergoing liver transplantation.[117]

Factor VIII and Hemophilia A–Related Liver Disease

Hemophilia A is a rare X-linked recessive bleeding disorder caused by the deficiency or absence of FVIII.[78,79] Because hemophilia etiology is heterogeneous (caused by different mutations in the F8 gene),[80] it is difficult to study the pathophysiology of hemophilia A–associated comorbidities. However, there are several reports of liver morbidities associated with hemophilia A.[76,81–83]

Infection with HCV is the most common liver pathophysiology associated with hemophilia A (seen mostly in patients age $\geq$60 y), which causes significant morbidity and mortality. Because of the requirement of blood derivatives, several patients with hemophilia were exposed to HCV infection in the past, until HCV testing became widely available. In addition, because of the occasional development of cirrhosis and HCC, hemophilia patients also are considered for liver transplantation.[118]

Although hepatitis C infection is the leading cause of most hemophilia-associated liver injuries, co-infection with HIV (owing to contamination of the plasma donor pool) also has been reported to accelerate the progression to end-stage liver disease in patients with hemophilia.[118,119]

HCC is another comorbidity associated with hemophilia. Older hemophilia patients are at increased risk for HCV-associated HCC and HIV-associated non-Hodgkin's lymphoma,[120] although the latter have been greatly reduced since the introduction of antiretroviral therapy in the mid-1990s. Age (>45 y), HCV or HIV infection, cirrhosis, and increased levels of α-fetoprotein are the risk factors for HCC development in hemophilia.[120] HCC is considered an important cause of mortality in patients with hemophilia, with a standardized mortality ratio of 17.2 (95% CI, 5.2–35.9).[121]

Bleeding from esophageal varices as a result of the lack of FVIII is another serious clinical morbidity in hemophilia A.[16,74] There are also increasing reports confirming the association of severe hemophilia A with the development of portal hypertension and age-induced organ injury.[81] A few clinical reports have shown the development of chronic persistent hepatitis with early cirrhosis in hemophilia patients.[82]

End-stage liver disease in hemophilia patients worsens with age.[121] However, liver biopsies are not performed routinely in these patients because of the increased risk of hemorrhage and the expense of a high dose of clotting factors. Thus, the pathophysiology of advanced liver diseases in hemophiliac patients remains largely unidentified.

Use of a Factor VIII–Deficient Murine Model to Study CLD

The FVIII-deficient murine model has been useful in studying the role and regulation of FVIII in CLDs. Using both a FVIII-deficient[22] and LMAN-deficient[23] (which impairs FVIII secretion) murine model, it was first shown that sinusoidal endothelial cells are the chief source of FVIII synthesis.

Loss of FVIII in mice was associated with low-grade hepatic inflammation. Expression of inflammatory markers such as tumor necrosis factor-α, CD45, and Toll-like receptor 4 were increased in the livers of FVIII-deficient mice.[22] Moreover, macrophage activation also was associated with FVIII loss, indicating that FVIII deficiency results in chronic inflammation in the liver, which could be the predominant cause for CLD progression in FVIII-deficient mice. A recent study also has shown the role of FVIII in NAFLD pathogenesis. The FVIII-deficient mice fed a high-fat diet developed hepatic steatosis, fibrosis, impaired energy metabolism, decreased platelet count, up-regulated de novo fatty acid synthesis, and lipid accumulation.[122]

FVIII deficiency also has been linked to liver regeneration after partial hepatectomy. Progressive loss of FVIII mRNA expression was shown to be associated with partial hepatectomy in mice.[92] However, plasma FVIII showed a significant increase along with a reduction of mRNA expression in the liver.[92] Increased FVIII protein in the plasma of the regenerating liver could be owing to a delay in the inactivation of plasma FVIII caused by increased VWF in plasma or decreased FVIII clearance in the liver. In addition, alteration of the intracellular trafficking of FVIII after a partial hepatectomy and the rapid release of FVIII from the storage sites also may contribute.

Conclusion and Future Directions

Studies over the past 2 decades have identified a prominent association of FVIII with CLDs. Several take-home messages have emerged from these provocative studies indicating the potential application of FVIII as a marker for inflammation, acute phase reactants, infection, and CLDs. Similarly, liver diseases with a reduced level of FVIII, such as acetaminophen-induced liver injury, hepatitis C, and acute liver failure, do benefit from FVIII replacement therapy with reduced bleeding risk, especially in patients with thrombocytopenia resulting from portal hypertension.

In considering the clinical implications of the findings related to FVIII in CLDs, it will be important to identify whether an increase in FVIII is an underlying cause or an effect of CLD-induced rebalanced hemostasis. FVIII, in

many circumstances, exerts context-dependent effects in settings of both chronic injury and coagulation defects, thus it remains unclear whether the increase in FVIII during later stages of CLDs is owing to impaired trafficking/degradation, inflammation, or increased synthesis. Similarly, the role of other coagulation components such as VWF, factor IX, or platelets in FVIII regulation during CLDs are not completely understood.

Therefore, it is possible that utilization of mice with FVIII deficiency and overexpression may yield mechanistic insight into the exact role of FVIII in CLDs. In conclusion, FVIII appears to be a viable and attractive biomarker for CLD that may be used to predict CLD-induced cirrhosis and hepatic failure. With respect to FVIII and CLD, there is a true opportunity for creative translation of basic research to the clinical setting.

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