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A Brief Overview about Thrombomodulin and Possible Role in Liver Cirrhosis

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Abstract: Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases. The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the most common causes in western countries, whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region. Soluble thrombomodulin (sTM) is yet another important marker of endothelial injury in liver cirrhosis. Thrombomodulin is typically present on the surface of endothelial cells and is involved in the regulation of blood coagulation. When endothelial cells are damaged or dysfunctional, they release sTM into the bloodstream as a response to injury. sTM can interact with thrombin and exhibits anticoagulant properties. Elevated sTM levels reflect endothelial injury and can contribute to the overall understanding of the severity of liver cirrhosis..

Keywords: Thrombomodulin, Liver Cirrhosis

Introduction: Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases. The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the most common causes in western countries, whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region **(1).**

Liver cirrhosis has many other causes, include inherited diseases such as hemochromatosis and Wilson's disease, primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Some cases are idiopathic or cryptogenic. In recent decades, NAFLD

has become a leading cause of chronic liver disease in Western countries such as the United States, with a prevalence of as high as 30% in the general population. Thus, NAFLD has attracted extensive attention as an important cause of chronic liver diseases **(2).**

Although the causes of liver cirrhosis are multifactorial, there are some pathological characteristics that are common to all cases of liver cirrhosis, including degeneration and necrosis of hepatocytes, and replacement of liver parenchyma by fibrotic tissues and regenerative nodules, and loss of liver function. Fibrosis as a precursor of cirrhosis is a pivotal pathological process in the evolution of all chronic liver diseases to cirrhosis **(3).**

At present, effective strategies to treat liver cirrhosis are still lacking, partially because of a poor understanding of the molecular mechanisms leading to cirrhosis. Thus, a better understanding of the pathogenesis of liver cirrhosis would facilitate the development of more effective treatment options (**4)**

Rates of cirrhosis vary widely across countries, with Egypt having the highest level (about 10-fold higher than that in other countries) The number of Egyptians estimated to be chronically infected with HCV is 9.8%, in addition to about more than 500,000 new infections annually. In addition to schistosomiasis, 50% of Schistosoma mansoni-infected population in Egypt is co HCV**.** Concomitant HCV and S. mansoni infection contributes to a higher incidence of hepatic cirrhosis, hepatocellular carcinoma, and a much higher liver related mortality rate **(5)**

Marker of Endothelial injury in liver cirrhosis:

Endothelial injury plays a significant role in the progression of liver cirrhosis. Several markers and factors are associated with endothelial injury in this condition. ***Some of these markers include*** **(6):**

von Willebrand Factor (vWF):

Elevated levels of von Willebrand Factor (vWF) serve as a critical marker of endothelial injury in liver cirrhosis. vWF is a glycoprotein produced and released by endothelial cells. In cirrhosis, the damaged endothelial cells release increased amounts of vWF into the bloodstream. This glycoprotein is integral to the blood clotting process and promotes platelet adhesion and aggregation at the sites of injury. As cirrhosis progresses, elevated vWF levels can contribute to a prothrombotic state, resulting in an increased risk of both bleeding and clotting complications **(7).**

Soluble P-selectin:

Soluble P-selectin is another key marker of endothelial injury in liver cirrhosis. P-selectin is an adhesion molecule expressed by endothelial cells, and in response to injury, activated endothelial cells release soluble P-selectin into the bloodstream. Elevated levels of soluble P-selectin indicate endothelial activation and the recruitment of platelets and inflammatory cells to the site of damage. This process is a common feature in cirrhosis, where inflammation and oxidative stress play a significant role **(8).**

Soluble Thrombomodulin (sTM):

Soluble thrombomodulin (sTM) is yet another important marker of endothelial injury in liver cirrhosis. Thrombomodulin is typically present on the surface of endothelial cells and is involved in the regulation of blood coagulation. When endothelial cells are damaged or dysfunctional, they release sTM into the bloodstream as a response to injury. sTM can interact with thrombin and exhibits anticoagulant properties. Elevated sTM levels reflect endothelial injury and can contribute to the overall understanding of the severity of liver cirrhosis **(8).**

Soluble VE-cadherin:

Soluble VE-cadherin is a notable marker that underscores endothelial injury in liver cirrhosis. VE-cadherin is a protein responsible for maintaining the integrity of endothelial cell junctions. When these junctions become disrupted, soluble VE-cadherin is released into the bloodstream, reflecting endothelial injury. The presence of soluble VE-cadherin indicates increased vascular permeability and compromised endothelial barrier function. This dysfunction contributes to complications seen in cirrhosis, including the leakage of fluids into the abdominal cavity, known as ascites **(9).**

Endothelin-1 (ET-1):

Endothelin-1 (ET-1) is a potent vasoconstrictor that plays a crucial role in the development of portal hypertension in liver cirrhosis. In cirrhosis, there is often an overexpression of ET-1 by endothelial cells, leading to increased vasoconstriction. This results in elevated pressure in the portal vein, which can cause complications such as variceal bleeding. Elevated levels of ET-1 are a marker of endothelial injury in cirrhosis and contribute to the understanding of the vascular abnormalities and heightened portal pressure in this condition **(10).**

Nitric Oxide (NO) and Endothelial Dysfunction:

Nitric oxide (NO) is a critical regulator of vascular tone and the maintenance of blood vessel flexibility. In liver cirrhosis, there is a disruption in the balance between NO production and substances that counteract its effects. This imbalance results in impaired vasoregulation, leading to vasoconstriction and increased portal pressure **(11).**

Endothelial Growth Factors:

Dysregulation of endothelial growth factors, such as vascular endothelial growth factor (VEGF), is an essential aspect of endothelial injury in cirrhosis. VEGF plays a critical role in angiogenesis and maintaining the integrity of blood vessels. In liver cirrhosis, there can be alterations in the expression of VEGF and its receptors. This can result in impaired angiogenesis, which is the formation of new blood vessels. Impaired angiogenesis can lead to reduced vascular density and perpetuate the ongoing endothelial injury observed in cirrhosis (**12).**

Oxidative Stress:

Oxidative stress is a condition where there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. In liver cirrhosis, oxidative stress can cause damage to endothelial cells, contributing to their dysfunction. As

a marker of endothelial injury, oxidative stress indicates that the endothelial cells are under duress due to the build-up of harmful reactive molecules **(13).**

Dysregulated Coagulation and Fibrinolysis:

Altered coagulation and fibrinolysis systems also impact endothelial function in liver cirrhosis. Changes in these systems can lead to endothelial injury and affect the balance between clot formation and dissolution. In cirrhosis, there is an increased risk of both bleeding and thrombosis **(14).**

Thrombomodulin

Thrombomodulin (TM) is a type-I transmembrane glycoprotein that was first discovered by Esmon and Owen in 1981 on endothelial cells as a cofactor for thrombin-catalyzed activation of protein C. This protein is encoded by an intronless gene (*THBD*) located on the chromosome 20p12-cen. Since its original identification, TM has also been found on a large variety of cells including macrophages, monocytes, platelets, neutrophils, and mesothelial cells. Endothelial TM is a made up of 557 amino acids with a molecular weight of approximately 74 kDa **(15).**

Structural Domains of Thrombomodulin:

There are five total domains that make up the total structure of mature TM. Starting from the *N* -terminus, these domains are the lectin-like domain (TMD1), epidermal growth factor (EGF)-like domain (TMD2), serine/threonine-rich domain (TMD3), transmembrane domain (TMD4), and a cytosolic tail (TMD5; . TM has multiple biological functions which are attributed to its different domains. The lectin-like domain of TM is similar in structure to C-type lectins but lacks a calcium-binding site (named as C-type lectin domain [CTLD]). This domain is involved in inflammation, tumor growth, and cell adhesion. It exerts anti-inflammation actions by binding proinflammatory stimuli before they can reach their target **(16).**

These include lipopolysaccharide (LPS) and high-mobility group box 1 protein. For its role in cell adhesion, the lectin-like domain can bind to fibronectin of the extracellular matrix. The TMD2 domain of TM contains six EGF-like repeats and is the site for TM's anticoagulation and fibrinolysis functions. These functions are allowed by TM's ability to activate protein C for anticoagulation, anti-inflammation, and thrombin activatable fibrinolytic inhibitor (TAFI) activation for fibrinolysis. Both of these processes require thrombin, which requires EGF56 for binding. It has been elucidated that the minimum structure for protein C activation is EGF456, while TAFI activation requires EGF3456. In addition to the coagulation function, the TMD2 domain has mitogenic activity, although the exact repeats needed for this activity is unknown **(8).**

Next, the TMD3 domain is a serine/threonine-rich domain which contains attachment sites for chondroitin sulfate (CS). There are two kinds of membrane TM, one with and one without CS. The CS moiety of TM is important for the enhancement of protein C activation by the thrombin–TM complex. The TMD4 domain anchors TM to the cell membrane and classifies

TM as a type-I membrane protein. The TMD5 domain is a small cytoplasmic tail region that plays a role in TM's ability to multimerize **(17).**

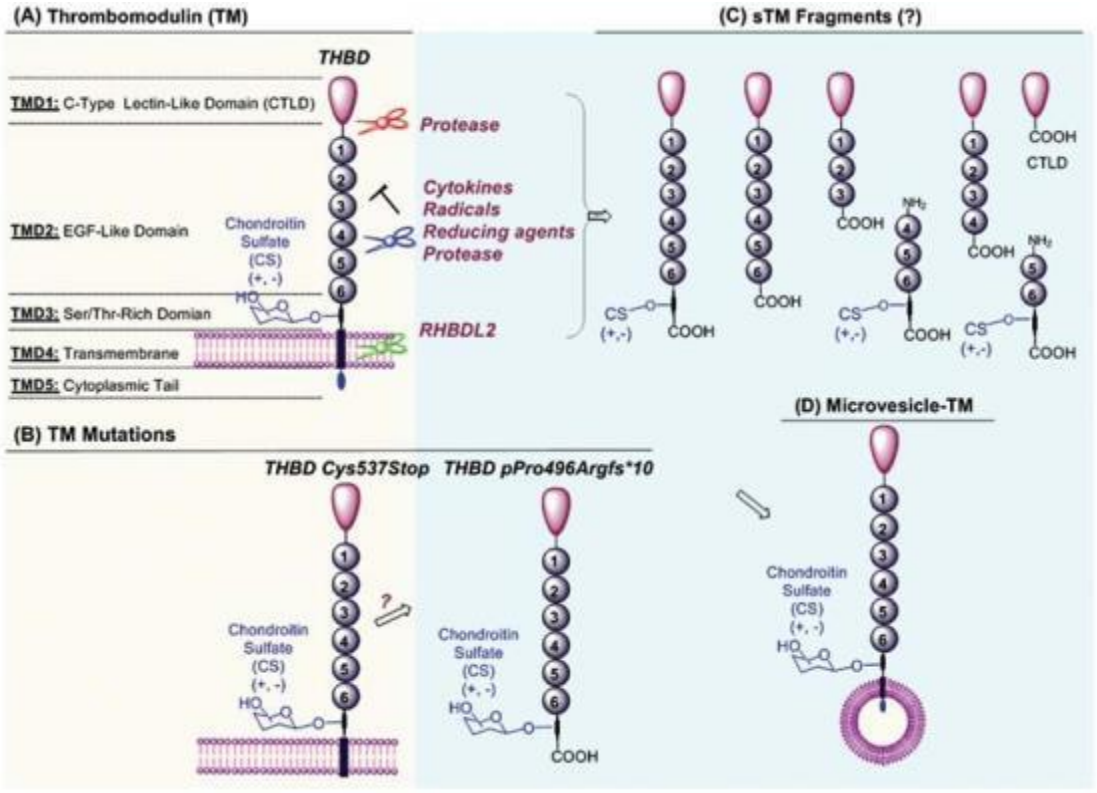

Figure (1): Schematic presentation of structural domains of membrane thrombomodulin (TM) (**A**) and TM mutations (**B**), its release mechanisms of predicted sTMs with corresponding domains (C), and microvesicle-TM (**C**). CS, chondroitin sulfate; CTLD, C-type lectin-like domain; EGF, epidermal growth factor; RHBDL2, the intramembrane protease rhomboid-like-2; Ser, serine; sTM, soluble thrombomodulin; Thr, threonine **(18).**

Circulating Thrombomodulin:

In addition to expression as a membrane protein on the cell surface, fragments of TM are also found circulating in the blood, urine, and other biofluids. These fragments of TM lack the transmembrane domain and are known as soluble TM (sTM). They are derived from membrane TM by cleavage via either proteolysis or chemical and physical stress. The sTM consists of fragments of different molecular weights whose presence can vary by disease. Different levels of sTM are found in many diseases. In addition, endothelial cells can release microvesicles (MVs) containing membrane TM (microvesicle-TM) which also contribute to circulating TM levels. Understanding of TM release mechanism is critical to comprehend its significance and role in disease development **(18).**

Measurement of the levels of circulating TM has great potential as a biomarker for diagnosis and tracking of different diseases. In this review, we summarize all these advances in three categories: (1) release mechanisms of circulating TM, (2) methods for measuring circulating TM in biological samples, and (3) correlation of circulating TM with diseases **(19).**

Release (Shedding) of Thrombomodulin:

In healthy humans, the levels of sTM are low (<10 ng/mL), while high sTM levels are common in patients suffering from various diseases. The mechanism responsible for sTM release is complex and several mechanisms have been proposed and confirmed. Primarily, TM is shed from the cell by enzymatic and/or chemical cleavage. It is known that endothelial TM serves as a cellular substrate for proteolytic cleavage, frequently leading to its shedding as various forms of **sTM (18).** Also, chemical cleavage of membrane-bound protein can generate sTM. Increased plasma sTM level has been accepted as a sensible marker for endothelial damage. In particular, the consistent elevation of sTM levels during pathologies is now widely regarded as an important circulatory biomarker for endothelial dysfunction and vascular risk assessment. It has been shown that sTM levels correlate with disseminated intravascular coagulation (DIC), stroke, multiple organ failure and mortality **(20).**

In addition, TM mutation that causes a synthesis of TM with the decreased size of the transmembrane domain can also contribute to the high levels of sTM in plasma. A new autosomal dominant bleeding disorder characterized by very high plasma levels of sTM has been reported, in which the *THBD* c.1611C > A (p.Cys537X) mutation in a heterozygous state was identified. The mutated TM lacks the last three amino acids of the transmembrane domain and the cytoplasmic tail and is associated with an increase in sTM in the plasma. On the other hand, activated endothelium can release microvesicles (and exosomes) containing membrane TM (microvesicle-TM). Overall, the mechanism responsible for TM shedding is complex and is not completely understood. Both the extracellular stimuli and a defect of synthesis of truncated TM contribute to the high levels of sTM in plasma. Understanding the mechanisms for TM shedding could help better understand underlying mechanisms of many diseases. This section summarizes various mechanisms for TM shedding known so far **(21).**

Functions of Thrombomodulin:

Thrombomodulin is a glycoprotein that plays a vital role in the regulation of blood coagulation and vascular health. It is primarily expressed on the surface of endothelial cells, which line the interior of blood vessels. Thrombomodulin has several essential functions **(22).**

- **Anticoagulation:**

One of the key functions of thrombomodulin is to act as an anticoagulant. When thrombin, a central enzyme in blood clot formation, comes into contact with thrombomodulin, it undergoes a conformational change. This altered thrombin no longer promotes clot formation but instead activates protein C **(20).**

- **Activation of Protein C:**

Thrombomodulin-bound thrombin activates protein C, another blood protein involved in coagulation regulation. Activated protein C (APC) inactivates coagulation factors Va and VIIIa, which are crucial for blood clot formation. By inhibiting these factors, thrombomodulin helps to prevent excessive blood clotting and maintains a balance in the coagulation system **(21).**

- **Endothelial Health:**

Thrombomodulin also plays a role in maintaining the health of endothelial cells. It has anti-inflammatory and anti-adhesive properties, which help to prevent excessive inflammation and the adhesion of blood cells to the vessel wall. This is important for preventing conditions like atherosclerosis **(22).**

- **Fibrinolysis:**

Thrombomodulin can enhance fibrinolysis, the process of breaking down blood clots. It can promote the activation of plasmin, an enzyme responsible for dissolving fibrin, a protein that forms the structural basis of blood clots **(23).**

- **Tissue Repair:**

Thrombomodulin is involved in tissue repair processes, including wound healing. It can modulate cell adhesion, migration, and proliferation, which are essential for tissue regeneration **(24).**

Thrombomodulin In Liver Diseases:

- **TM expression in Liver**

The liver regulates the most chemical levels in the blood by breaking down or converting certain substances. There are considerations on liver function as predictors of Soluble TM (sTM) levels. Therefore, there is a correlation between sTM levels and liver diseases as well. Plasma sTM levels were often evaluated in patients with liver diseases. TM expression in hepatic endothelial cells are highly affected in liver diseases like viral hepatitis and liver damage which also cause sTM release. Overall, liver enzymes could be modulators of sTM and sTM levels as well. The increase in plasma sTM levels in liver disease may be due to defective hepatic degradation of the circulating sTM. On the other hand, higher level or activity of liver enzymes may cause decreased plasma sTM levels. It is not known how liver function and dysfunction influence sTM levels. The plasma sTM levels and liver diseases deserve further mechanistic study **(8).**

Endothelial cells produce the transmembranous glycoprotein TM. Except for the brain, TM is found in all human arteries, veins, capillaries, and lymphatics. Acting as a scaffold for thrombin, TM accelerates the activation of protein C and accordingly accelerates degrading factor Va and factor VIIIa, thereby, restraining the coagulation reactions and restricting fibrin formation. So, TM mediates the antifibrinolytic effect at a lower level and the profibrinolytic effect at a higher level. When endothelium cells were injured by inflammation, increased shear stress, or other factors, TM shed into plasm from the surface and formed sTM whose molecular weights were much lower than cellular TM. There were 4–6 fragments of sTM with different molecular weights but a similar anticoagulation function to TM. The liver and kidney cleared sTM, and it was found in both plasma and urine **(25).**

- **sTM as marker of endothelial cell injury:**

Several studies verified that sTM was a sensitive marker of endothelial cell injury. It was found when umbilical vein endothelial cells were treated with N-formyl-methionyl-leucy-phenylalanine or lipopolysaccharide (LPS), sTM in the medium increased in a time-dependent manner and paralleled with the extent of cell damage. When culture mediums were supplemented with hydrogen peroxide, neutrophil proteases proteinase-3, elastase, or cathepsin G, it was discovered that sTM increased rapidly. The authors hypothesized that sTM was released rather than secreted by injured endothelial cells and that it could be used as both an early and advanced stage marker. Other studies observed similar results **(26).**

A recent study characterized circulating plasma MVs profile in patients with decompensated cirrhosis and AKI. They found that patients with cirrhosis with AKI had a significantly higher level of total MVs compared with patients with cirrhosis without AKI but comparable severity of underlying liver disease. They concluded that AKI is responsible for the increased levels of MVs observed in patients with cirrhosis **(27).**

As a reliable marker of endothelial cell injury, sTM was found to be related to many vascular-associated diseases, such as CHD, renal failure, disseminated intravascular coagulation, vasculitis, etc. In a cohort of sepsis with and without acute kidney injury, the plasma sTM was 23.6 U/ml vs. 15.6 U/ml, respectively, ($P < 0.001$) and served as an independent predictive factor rather than E-selectin, PAI-1, and protein C.

In a case–control study, sTM was found to have an inverse relationship with a CHD occurrence. It was found that lower sTM tertile amplified the CHD risk of higher fibrinogen. It was found that sTM level increased significantly paralleled from the control group, stable angina, and acute coronary syndromes group. A similar result was also reached by Mezaki T **(8).**

sTM is also a marker of LSECs injury. In a previous study, sTM and the expression of sinusoidal TM increased during acute liver injury induced by D-galactosamine, especially in the necrotic area and around the central vein, suggesting that sTM was related to endothelial injury and parenchymal necrosis **(28).**

Several studies had previously determined sTM in various liver diseases, but the results were inconsistent. In a case–control study, sTM was elevated in hepatocellular carcinoma patients (42.1 ± 2.0 ng/ml) than in cirrhosis patients (28.3 ± 2.1 ng/ml; $P = 0.039$), and sTM level did not relate to the outcome of cirrhosis individuals **(8).**

Two kinds of ELISA methods was used to detect plasma sTM. They found that sTM, including all fragments of sTM, increased in acute liver failure patients. sTM, on the other hand, remained stable in cirrhosis patients, whereas the ratio of smaller sTM to larger sTM decreased. In chronic hepatitis and early cirrhosis, the plasma sTM maintained similar to healthy controls **(8).**

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